25

Office of the CEO & Chairman of the Board
201 Technology Dr. • Irvine • California • 92618
Main Line: (949) 450-5400
Facsimile: (949) 450-5319
Website: www.endocare.com

VIA FEDERAL EXPRESS

September 20, 2006

Mark B. McClellan, MD, PhD
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Attention: CMS-1506-P
Mail Stop C4-26-05
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: CMS-1506-P, Medicare Program; Hospital Outpatient Prospective Payment System and CY 2007 Payment Rates; Proposed Rule

Dear Dr. McClellan:

On behalf of Endocare, Inc., I am writing in response to the Proposed Rule for the CY 2007 Medicare Hospital Outpatient Prospective Payment System, published in the *Federal Register* on August 23, 2006. Endocare is a medical device company focused on the development, manufacturing and distribution of minimally invasive cryoablation technologies that utilize our patented technologies to freeze and thereby, ablate tissue and tumors in patients with cancer.

Proposed Assignment of CPT Code 0135T, *Percutaneous Cryoablation of Renal Tumors* to APC 423; Payment Rate for APC 423

We applaud CMS's policy of recognizing new Category III CPT codes and assigning them to APCs—either New Technology APCs or established clinical APCs. As CMS noted in the 2006 Final Rule, this proactive stance in addressing these new codes will serve both to avoid a delay in beneficiary access to the new service and to further the collection of procedure cost and utilization data.

Further, we appreciate the fact that the proposed rule reassigns the new CPT tracking code for percutaneous cryoablation of renal tumors (CPT 0135T) from APC 163 to a more appropriate clinical APC, APC 423, grouping it with a similar procedure, radiofrequency percutaneous ablation for renal tumors (CPT 47382). We believe this reassignment now groups "like procedures with like procedures."

endocare
extending life everyday

Office of the CEO & Chairman of the Board
201 Technology Dr. • Irvine • California • 92618
Main Line: (949) 450-5400
Facsimile: (949) 450-5319
Website: www.endocare.com

While this proposed reassignment of CPT 0135T groups clinically similar percutaneous ablation procedures into the same APC, the payment rate assigned to APC 423 is not based on any actual cost data associated with performing CPT 0135T, and therein lies the problem. APC 423 does not cover the costs hospitals incur in providing the renal cryoablation procedure. In fact, the proposed payment rate for APC 423 does not even cover hospital acquisition costs for the CryoProbes used in the renal cryoablation procedure. We have detailed these costs below, and recommend that CMS adjust the payment rate for APC 423 in light of these actual costs and this analysis.

We believe, as a matter of policy, that it is appropriate—and imperative—for CMS to accept this information and use it as the rationale to re-price APCs which contain new procedures when there are no hospital claims data available to calculate and set a pricing decision.

Background on Percutaneous Cryoablation

Percutaneous cryoablation is growing as a minimally invasive treatment option for patients with renal cell carcinoma. Other treatment options for these tumors include surgical removal and radiofrequency ablation.

- Percutaneous cryoablation is a technique to ablate the tumor by freezing the cells via a probe placed percutaneously in or around the renal tumor.

- Percutaneous cryoablation procedures are generally performed in the hospital radiology imaging suite with CT or MRI image guidance; occasionally, the procedure is performed with ultrasound (US) guidance. CT/MRI/US images are used to monitor the probe placement and the development of the ice ball, which freezes the tumor. These imaging technologies are also used to monitor adjacent structures during the cryoablation procedure.

- Cell death is caused by direct freezing, cell dehydration, and ischemic hypoxia. The percutaneous cryoablation procedure generally involves two freeze and thaw cycles; the procedure requires from 90 minutes to three hours to perform, depending on the complexity of the case.

- Generally, 2-3 CryoProbes are used in each renal cryoablation procedure (average use is 2.5 probes per procedure). These probes are uniquely designed for percutaneous procedures to fit into a CT gantry. The acquisition cost to hospitals is typically more than $1,000 per probe, for a conservative total of $2,000 - $3,000 per case in probe costs alone. (These hospital costs represent Endocare's experience, illustrated by the enclosed de-identified cancelled checks for sales made to hospitals in 2005).

endocare
extending life everyday

Office of the CEO & Chairman of the Board
201 Technology Dr. • Irvine • California • 92618
Main Line: (949) 450-5400
Facsimile: (949) 450-5319
Website: www.endocare.com

- Currently, about 60-70 percent of these cases are performed on an outpatient basis.

Though cryoablation and radiofrequency percutaneous ablation procedures for renal tumors are closely aligned clinically, the major resource difference between these two procedures, which are proposed to be grouped together in APC 423 in CY 2007, relates to the equipment and number of probes used. The radiofrequency procedure involves the use of only one probe, while the cryoablation procedure requires, on average, 2.5 probes.

Recommendation

We ask that CMS re-price APC 423 by taking into consideration the following facts concerning the resources required for renal cryoablation procedures performed in the hospital outpatient setting:

- Probe Costs. The costs hospitals incur in acquiring the probes used in performing percutaneous cryoablation for renal tumor procedures approximate the proposed payment rate for APC 423 (e.g., $2,402). We are enclosing cancelled checks documenting that the average payment per CryoProbe used in renal cryoablation procedures is >$1,000. We have also enclosed a copy of a presentation made to CMS staff in December 2005 in which the average probe usage of 2.5 probes per case was documented. This information demonstrates that over $2,500 in probe costs alone is incurred by hospitals for each renal cryoablation procedure.

- Other Hospital Costs. Apart from the cost of probes, other hospital procedure costs, including staffing and supply expenses associated with the case, as well as procedure time, needs to be considered—and included—into any calculation of the total costs incurred by hospitals in performing procedures for the percutaneous cryoablation for renal tumors. While we have no firm data on these costs, and there is no claims data from the Medicare claims system to date, we suggest CMS use the non-probe procedure costs of radiofrequency percutaneous ablation procedures for renal tumors (CPT 47382), which are also assigned to APC 423. We estimate these costs to be in excess of $1,500 per procedure.

We recognize the difficulties in setting prices for new procedures—given the lack of hospital data on the costs associated with new medical procedures, particularly, those identified by Category III CPT codes, like renal cryoablation. If CMS chooses to assign a new procedure to a clinical APC instead of a New Technology APC, it should, as a matter of policy, utilize all available data (including external data) to factor in the costs hospitals incur in providing the new procedures.

endocare
extending life everyday

Office of the CEO & Chairman of the Board
201 Technology Dr. • Irvine • California • 92618
Main Line: (949) 450-5400
Facsimile: (949) 450-5319
Website: www.endocare.com

We believe that the data we have provided on CryoProbe cost and utilization in percutaneous renal cryoablation procedures shows that the proposed payment rate for APC 423 is not adequate. There is no doubt that this underpayment will act as a disincentive for hospitals to offer this procedure. This disincentive will create an access barrier to this minimally invasive, clinically effective procedure for Medicare patients. We urge you to re-price this APC, with the information we have supplied, so that the treatment of renal cell carcinoma is made based on clinical—and not payment—grounds.

Thank you for allowing Endocare the opportunity to comment on this proposed rule. Please do not hesitate to contact me if you have questions or require additional information.

Sincerely,

Craig T. Davenport
Chief Executive Officer
Chairman of the Board

Enclosures
CTD:res

Attachment

De-Identified Invoices & Cancelled Checks Illustrating Hospital Expense for Renal Probes

2005

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

#1

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0014476-IN
INVOICE DATE: 11/09/2005

ORDER NUMBER: 0012487
ORDER DATE: 11/09/2005
SALESPERSON: 0012
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted]

CONFIRM TO:
Osi

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
181	UPS GROUND	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG	EACH	1 WHSE: 000	1	0	1,250.00	1,250.00
R1.7 CRYOPROBE, RENAL, 1.7MM	EACH	1 WHSE: 000	1	0	1,250.00	1,250.00

paid
CK# 7533
dtd 11/14/05

Fax (866) 313-3636

Net Invoice:	2.500.00
Less Discount:	0.00
Freight:	5.07
Sales Tax:	0.00
Invoice Total:	**2,505.07**

Endocare

7533

Check Number: 7533
Check Date: Nov 10, 2005

Check Amount: $2,380.07

Invoice	Date	Discount Taken	Amount Paid	Quantity	Description
014476-IN	11/10/05	125.00	2380.07	1.00	RenalCryo 3.8mm Angled Probe - oblong ice - long shaft
				1.00	1.7mm Renal Probe Sharp Tip - Oblong Ice
				1.00	Freight

[redacted]

[redacted]

Check Number: 7533

88-200/1119

7533

DATE
Nov 10, 2005

Memo: 00 - [redacted]

AMOUNT
$ 2380.07

Two Thousand Three Hundred Eighty and 07/100 Dollars

THE ORDER OF

Endocare
201 Technology Drive
Irvine, CA 92618

Security features. Details on back.

⑈007533⑈ ⑆111902000⑆323000301 2⑈

Bok 5% discount

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

#2

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0014359-IN
INVOICE DATE: 10/31/2005

ORDER NUMBER: 0012446
ORDER DATE: 10/28/2005
SALESPERSON: 0351
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted] Medical Center
[redacted]

CONFIRM TO:
Stacy Kjeldgaard

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
101105-CO	HANDCARRY	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
CRYO-206-F PROCEDURE KIT 2.4MM PROBES	EACH	1 WHSE: 115	1	0	2,700.00	2,700.00
CRYO-44-F CRYOPROBE, 2.4MM	EACH	2 WHSE: 115	2	0	900.00	1,800.00
R3.8 CRYOPROBE, RENAL, 3.8MM	EACH	1 WHSE: 115	1	0	2,500.00	2,500.00
R2.4 CRYOPROBE, RENAL, 2.4MM	EACH	1 WHSE: 115	1	0	2,500.00	2,500.00

DOS: 10/11/05; [redacted]

DOS: 10/11/05; [redacted]

Do not ship. Hand delivered by rep.

CK# 127701
11/28/05

Fax (866) 313-3636

Net Invoice:	9.500.00
Less Discount:	0.00
Freight:	0.00
Sales Tax:	130.50
Invoice Total:	**9,630.50**

P1001 ENDOCARE [E0969]

CHECK DATE CHECK NO.
11/22/2005 000127701

DOC NO	APPLY TO	DATE	VENDOR CREDIT NO	VENDOR INVOICE NO	DOC AMOUNT	DISCOUNT	PAYMENT AMOUNT
000127701	000297153	10/31/2005		0014385-IN HEARTCO	2,778.30	0.00	2,778.30
000127701	000297266	10/31/2005		0014358-IN HTCPYO	2,700.00	0.00	2,700.00
000127701	000297268	10/31/2005		0014359-IN HTCPYO	9,630.50	0.00	9,630.50
							15,108.80

[redacted]

THE FACE OF THIS DOCUMENT HAS A COLORED BACKGROUND ON WHITE PAPER

[redacted]

BANK OF AMERICA, N.A.
WICHITA FALLS, TEXAS
86-130/1119

CHECK NO
000127701

KIMBERLY 11/22/2005

DATE	AMOUNT
11/22/2005	******15,108.80

Void after 90 days

y FIFTEEN THOUSAND ONE HUNDRED EIGHT AND 80/100 DOLLARS

The
der

ENDOCARE
201 TECHNOLOGY DR.
IRVINE, CA 92618

John Q. Barnidge
James D. Clark

AUTHORIZED SIGNATURE THIS CHECK CLEARS POSITIVE PAY

PRINTED ON THE BACK OF THIS CHECK IS A SECURITY SCREEN

⑈127701⑈ ⑆121901302⑆ 0023300 28183⑈ ⑈0001510880⑈

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#3)

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0013368-IN
INVOICE DATE: 08/26/2005

ORDER NUMBER: 0012223
ORDER DATE: 08/25/2005
SALESPERSON: 0022
CUSTOMER NO: 00[redacted]

[redacted]

[redacted]

CONFIRM TO:
Renee Howell

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
4500456817	HANDCARRY	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG DOS: 6/28/05; [redacted]	EACH	1 WHSE: 043	1	0	2,750.00	2,750.00

Do not ship. Hand delivered by rep.

CK#
80007630
11/18/05

Fax (866) 313-3636

Net Invoice:	2.750.00
Less Discount:	0.00
Freight:	0.00
Sales Tax:	0.00
Invoice Total:	**2,750.00**

[redacted]

Bank of America

VENDOR ACCOUNT

52-153
112

CHECK NO: 80007630

CHECK VOID AFTER 180 DAYS

DATE	PAYMENT AMOUNT
11/14/2005	**********$2,750.00

PAY ***Two thousand seven hundred fifty and 00/100 Dollars***

TO THE ORDER OF:

ENDOCARE INC (CRYO-PRODUCTS)
201 TECHNOLOGY DR
IRVINE, CA 92618 US

TWO SIGNATURES REQUIRED FOR AMOUNTS $100,000 AND OVER

⑈80007630⑈ ⑆011201539⑆ 00222000220 2⑈

[redacted] MEDICAL CENTER

[redacted]

Payment Method	C	Check Number	80007630
Vendor Number	0000110325	Date	11/14/2005

DATE	INVOICE NO.	DOCUMENT NO.	GROSS	DISCOUNT	NET AMOUNT
09/26/2005	13368IN	1951005543	2,750.00	0.00	2,750.00
		TOTAL	2,750.00	0.00	2,750.00

[redacted]

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#4)

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0014181-IN
INVOICE DATE: 10/21/2005

ORDER NUMBER: 0012422
ORDER DATE: 10/21/2005
SALESPERSON: 0012
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted]

CONFIRM TO:
[redacted]

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
PO-102105-HTCKS	UPS BLUE	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG	EACH	2 WHSE: 000	2	0	2,500.00	5,000.00
R1.7 CRYOPROBE, RENAL, 1.7MM	EACH	3 WHSE: 000	3	0	1,750.00	5,250.00
R2.4 CRYOPROBE, RENAL, 2.4MM	EACH	2 WHSE: 000	2	0	2,500.00	5,000.00

CK# 1041
11/17/05

Fax (866) 313-3636

Net Invoice:	15,250.00
Less Discount:	0.00
Freight:	70.29
Sales Tax:	0.00
Invoice Total:	**15,320.29**

ENTITY VENDOR
P3811 ENDOCARE EXTENDING LIFE [E1000]

CHECK DATE CHECK NO.
11/11/2005 000001041

DOC NO	APPLY TO	DATE	VENDOR CREDIT NO	VENDOR INVOICE NO	DOC AMOUNT	DISCOUNT	PAYMENT AMOUNT
000001041	000000186	10/03/2005		0013979-IN	40,581.65	0.00	40,581.65
000001041	000000212	10/21/2005		0014181-IN	15,320.29	0.00	15,320.29
							55,901.94

[redacted]

THE FACE OF THIS DOCUMENT HAS A COLORED BACKGROUND ON WHITE PAPER

[redacted]

BANK OF AMERICA
[redacted]
32-2/1110

CHECK NO
000001041

DATE	AMOUNT
11/11/2005	******55,901.94

Void after 90 days

Pay FIFTY FIVE THOUSAND NINE HUNDRED ONE AND 94/100 DOLLARS

To The Order Of

ENDOCARE EXTENDING LIFE
EVERYDAY
201 TECHNOLOGY DR.
IRVINE, CA 92618

John Q. Barnidge
James D. Clark

AUTHORIZED SIGNATURE THIS CHECK CLEARS POSITIVE PAY

PRINTED ON THE BACK OF THIS CHECK IS A SECURITY SCREEN

⑈000104⑈ ⑆111000025⑆ 0048106 23958⑈ ⑈0005590194⑈

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#5)

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0013077-IN
INVOICE DATE: 07/29/2005

ORDER NUMBER: 0012138
ORDER DATE: 07/29/2005
SALESPERSON: 0084
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted]

CONFIRM TO:
[redacted]

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
10074	HANDCARRY	IRVINE	Net 60 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
CRYO-206-F PROCEDURE KIT 2.4MM PROBES	EACH	1 WHSE: 084	1	0	2,000.00	2,000.00
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG	EACH	1 WHSE: 084	1	0	2,000.00	2,000.00

DOS: 7/20/05; P[redacted]

DOS: 7/20/05; P[redacted]

Do not ship. Hand delivered by rep.

Ck# 1557 10/21/05
1571 10/31/05

Fax (866) 313-3636

Net Invoice:	4.000.00
Less Discount:	0.00
Freight:	0.00
Sales Tax:	0.00
Invoice Total:	**4,000.00**

[redacted]

[redacted]

101-7270/2215

1557

10/14/2005

THE ORDER OF Endocare, Inc

$ **6,000.00

Six Thousand and 00/100********** DOLLARS

Endocare, Inc
201 Technology Drive
Irvine, CA 92618

VOID AFTER 60 DAYS

AUTHORIZED SIGNATURE

Security features. Details on back.

⑈001557⑈ ⑆122157270⑆ 24⑈040080595⑈

1557

[redacted]

Endocare, Inc

TECH101

10/14/2005

Date	Type	Reference	Original Amt.	Balance Due	Discount	Payment
5/20/2005	Bill	0012019-IN	2,000.00	2,000.00		2,000.00
6/8/2005	Bill	0012141-IN	2,000.00	2,000.00		2,000.00
8/8/2005	Bill	0013077-IN	4,000.00	4,000.00		2,000.00
					Check Amount	6,000.00

6,000.00

WesternBank Checkin

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#6)

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0013863-IN
INVOICE DATE: 09/29/2005

ORDER NUMBER: 0012342
ORDER DATE: 09/29/2005
SALESPERSON: 0369
CUSTOMER NO: 00-F[redacted]

[redacted]

[redacted]

CONFIRM TO:
Emma Guyton

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
146440	UPS RED	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG	EACH	6 WHSE: 000	6	0	1,250.00	7,500.00

Ck# 455443
10/26/05

Fax (866) 313-3636

Net Invoice:	7,500.00
Less Discount:	0.00
Freight:	78.40
Sales Tax:	0.00
Invoice Total:	**7,578.40**

NO. 455443

RE INC, 201 TECHNOLOGY DRIVE, IRVINE CA 92618-2400

Date: 10/21/2005

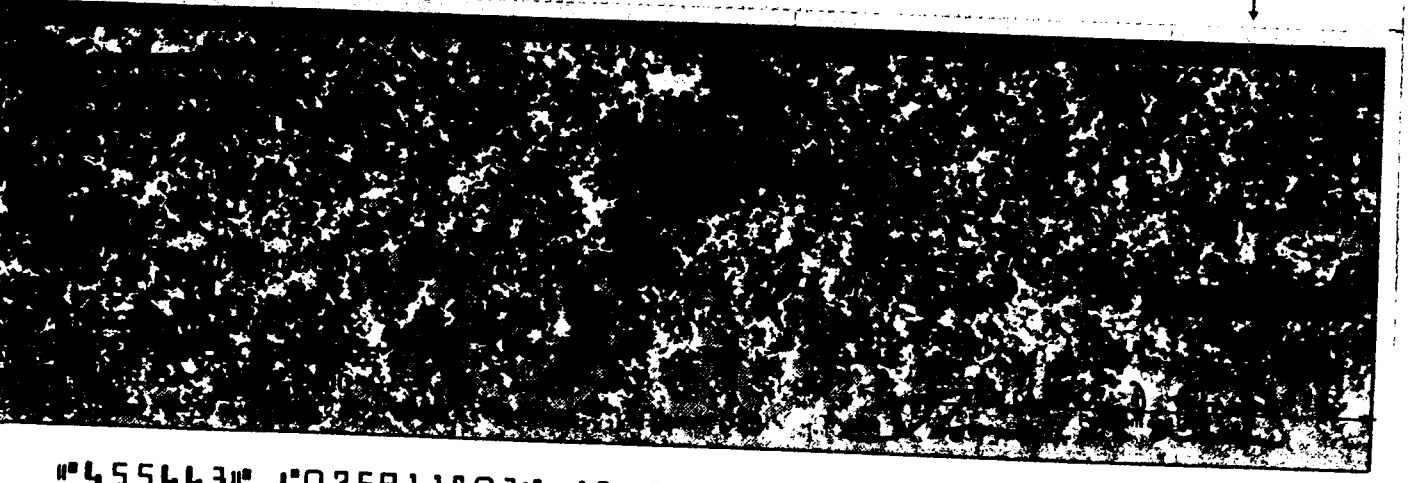
Vendor No. 5515

Invoice	PO	Description	Date	Gross Amount	Discount Amount	Net Amount Paid
0013474IN	800165		08/31/05	$6,000.00		$6,000.00
0013863IN	146440		09/29/05	$7,578.40		$7,578.40
		80FR0001				
			TOTALS:	$13,578.40	$0.00	$13,578.40

Page 1 of 1

Detach at Perforation Before Depositing Check

REMOVE DOCUMENT ALONG THIS PERFORATION



"455443" :075911603: 16"733"7"

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#1)

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0013133-IN
INVOICE DATE: 08/09/2005

ORDER NUMBER: 0012167
ORDER DATE: 08/09/2005
SALESPERSON: 0012
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted]

CONFIRM TO:
Judy Wagner

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
2670824	UPS RED	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG	EACH	6 WHSE: 000	6	0	1,750.00	10,500.00

CR# 1327126

9-12-05

Fax (866) 313-3636

Net Invoice:	10.500.00
Less Discount:	0.00
Freight:	78.95
Sales Tax:	0.00
Invoice Total:	**10,578.95**

[redacted]

REMITTANCE STATEMENT

For inquiries call [redacted]

VENDOR NAME: ENDOCARE INC

CHECK NUMBER: 1327126

VENDOR NUMBER: 45006

INVOICE NUMBER	MEMO	INVOICE DATE	P.O. NUMBER	GROSS AMOUNT	DISCOUNT	NET AMOUNT
0013133-IN	sl	08/09/05	2670824	10578.95	0.00	10578.95

10-CLE0001

RECEIVED
SEP 12 2005
By _____

TOTALS	10578.95	0.00	10578.95

PLEASE DETACH HERE AND RETAIN THIS PORTION FOR YOUR RECORDS

▼ Detach at perforation below ▼

[redacted]

Controlled Disbursement Account

56-389
412

Vendor Number	Check Date	Check Number
45006	09/08/05	1327126

TEN THOUSAND FIVE HUNDRED SEVENTY EIGHT US DOLLARS AND 95/100 ***

$10,578.95

PAY TO THE ORDER OF
ENDOCARE INC
201 TECHNOLOGY DR
IRVINE CA 92618

⑈1327126⑈ ⑆041203895⑆0150973⑈

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

HS

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0012610-IN
INVOICE DATE: 06/29/2005

ORDER NUMBER: 0012025
ORDER DATE: 06/29/2005
SALESPERSON: 0092
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted]

CONFIRM TO:
Henry

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
22498	UPS RED AM	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R1.7 CRYOPROBE, RENAL, 1.7MM	EACH	1 WHSE: 000	1	0	1,000.00	1,000.00
CRYO-103 PROCEDURE KIT	EACH	1 WHSE: 000	1	0	4,750.00	4,750.00
CRYO-2.4S CRYOPROBE, 2.4MM (SHORT-ICE)	EACH	6 WHSE: 000	6	0	0.00	0.00
CRYO-74 FAST TRAC ACCESS SET - 2MM	EACH	1 WHSE: 000	1	0	0.00	0.00
CRYO-55-F TEMPPROBE, SHORT	EACH	5 WHSE: 000	5	0	0.00	0.00
CRYO-60 CIRCULATING CATH/TUBE KIT	EACH	1 WHSE: 000	1	0	0.00	0.00
CRYO-51 DRAPE & GOWN PACK	EACH	1 WHSE: 000	1	0	0.00	0.00

CK#
280439
8/10/05

Fax (866) 313-3636

Net Invoice:	5.750.00
Less Discount:	0.00
Freight:	89.62
Sales Tax:	391.88
Invoice Total:	**6,231.50**

[redacted]

01281 ENDOCARE INC

280439

INVOICE NO.	DATE	GROSS AMOUNT	MEMO	DISCOUNT AMOUNT	NET PAYABLE
0012610-IN 75	06/29/05	6,231.50			6,231.50
			00-ALH ΦΦ1		
CHECK NO. 280439 08/03/05	TOTALS	6,231.50	TOTALS		6,231.50

[redacted]

280439

INVOICE NO.	DATE	GROSS AMOUNT	MEMO	DISCOUNT AMOUNT	NET PAYABLE
0012610-IN 75	06/29/05	6,231.50			6,231.50
CHECK NO. 280439	[redacted]	6,231.50	[redacted]		6,231.50

[redacted]

280439 90-3957/1222

VOID AFTER 6 MONTHS

01281 280439

DATE 08/03/05

AMOUNT $6,231.50

Six Thousand Two Hundred Thirty-One Dollars and Fifty Cents

AY
O THE
RDER
F

ENDOCARE INC
201 TECHNOLOGY DRIVE
IRVINE CA 92618

AUTHORIZED SIGNATURE

AUTHORIZED SIGNATURE

⑈280439⑈ ⑆122395711⑆ 001 037056⑈

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

#9

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0012474-IN
INVOICE DATE: 06/23/2005

ORDER NUMBER: 0011989
ORDER DATE: 06/23/2005
SALESPERSON: 0114
CUSTOMER NO: 51[redacted]

[redacted]

[redacted]

CONFIRM TO:
Eddie Cranor

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
419583	UPS RED	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
PERC-24 CRYOPROBE, IR, 2.4MM	EACH	6 WHSE: 000	6	0	1,000.00	6,000.00
R3.8L CRYOPROBE, RENAL, 3.8MM, LONG	EACH	3 WHSE: 000	3	0	2,500.00	7,500.00

CR# 2200927

7/28/05

Fax (866) 313-3636

Net Invoice:	13.500.00
Less Discount:	0.00
Freight:	90.72
Sales Tax:	465.00
Invoice Total:	**14,055.72**

THE FACE OF THIS DOCUMENT HAS A COLORED BACKGROUND ON WHITE PAPER

[redacted]

[redacted]

CHECK NO. 2200927

70-2328
0719

P.O. Box 160727
Sacramento, CA 95816-0727

DATE 07/22/05

CHECK AMOUNT *******14,055.72

Fourteen thousand fifty five and 72/100 Dollars

PAY TO THE ORDER OF

ENDOCARE INC
201 TECHNOLOGY DR
IRVINE CA 92618

THE BACK OF THIS DOCUMENT CONTAINS AN ARTIFICIAL WATERMARK-HOLD AT ANGLE TO VIEW

⑈000220092 7⑈ ⑆071923284⑆ 87659⑈02218⑈

[redacted]

DATE	COMPANY NO.	PROCESS LEVEL	VENDOR NO.	CHECK NO.
07/22/05	110		28391	2200927

DATE	INVOICE OR CREDIT MEMO NUMBER	TYPE	DESCRIPTION	REF NO	GROSS	DISCOUNT AMOUNT	NET
06/23/05	0012474IN		51- [redacted]		14,055.72		14,055.72
				TOTAL	$14,055.72	0.00	$14,055.72

THE ATTACHED CHECK IS IN PAYMENT FOR ITEMS DESCRIBED ABOVE.

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#10)

INVOICE NUMBER: 0012127-IN
INVOICE DATE: 05/26/2005

ORDER NUMBER: 0011610
ORDER DATE: 05/24/2005
SALESPERSON: 0012
CUSTOMER NO: 00-[redacted]

201 Technology
Irvine, CA 92618
(949) 450-5400

[redacted]

[redacted]

CONFIRM TO:
Mary Walker

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
508009	HANDCARRY	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R2.4L	EACH	1	1	0	2,500.00	2,500.00
CRYOPROBE, RENAL, 2.4MM, LONG		WHSE: 043				

DOS: 4/19/05; Patient: [redacted]

Do Not Ship. Delivered by Rep.

CK# 138779
7-14-05

Fax (866) 313-3636

Net Invoice:	2.500.00
Less Discount:	0.00
Freight:	0.00
Sales Tax:	0.00
Invoice Total:	**2,500.00**

[redacted]

138779

Date: 07/06/05

62-22
311

TO THE ORDER OF: ENDOCARE INC
201 TECHNOLOGY DRIVE
IRVINE CA 92618

$ ***** 13,000.00

THIRTEEN THOUSAND AND 00/100---------- DOLLARS

[redacted]

⑈138779⑈ ⑆031100225⑆ 207995008406 6⑈

[redacted]

07/06/05 DATE | 138779 CHECK NO.

13,000.00 CHECK AMOUNT

ENDOCARE INC
201 TECHNOLOGY DRIVE
IRVINE CA 92618

INVOICE DATE	INVOICE NUMBER	P.O. NBR.	DESCRIPTION	AMOUNT	DISCOUNT	NET AMOUNT
05/25/05	0012083-IN	508011		3500.00	0.00	3500.00
05/26/05	0012127-IN	508009		2500.00	0.00	2500.00
05/26/05	0012129-IN	508024	00 - capital	7000.00	0.00	7000.00

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

#11

INVOICE NUMBER: 0012418-IN
INVOICE DATE: 06/17/2005

201 Technology
Irvine, CA 92618
(949) 450-5400

ORDER NUMBER: 0011930
ORDER DATE: 06/16/2005
SALESPERSON: 0092
CUSTOMER NO: 00[redacted]

[redacted]

[redacted]

CONFIRM TO:
Katie Limon

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
5-17928	HANDCARRY	IRVINE	Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
R1.7	EACH	1	1	0	1,250.00	1,250.00
CRYOPROBE, RENAL, 1.7MM		WHSE: 352				
R2.4L	EACH	2	2	0	1,500.00	3,000.00
CRYOPROBE, RENAL, 2.4MM, LONG		WHSE: 352				

DOS: 6/8/05; Patient: [redacted]z

Do Not Ship. Delivered by Rep.

CK. #
205 3880
7/7/05

Fax (866) 313-3636

Net Invoice:	4.250.00
Less Discount:	0.00
Freight:	0.00
Sales Tax:	329.38
Invoice Total:	**4,579.38**

PAY TO THE ORDER OF

07/01/2005 552 2053880

ENDOCARE
201 TECHNOLOGY DR
IRVINE, CA 92618

$4,579.38

********** Four Thousand Five Hundred Seventy-Nine and 38/100 Dollars

M 0252900

Drawn on
Wachovia Bank, N.A., Greenville, South Carolina
In cooperation with & payable if desired at Wells Fargo Bank, N.A.
4759-606858

⑈002053880⑈ ⑆053200019⑆ 2079971051955⑈

THE ORIGINAL DOCUMENT HAS A WHITE REFLECTIVE WATERMARK ON THE BACK. HOLD AT AN ANGLE TO SEE THE MARK WHEN CHECKING THE ENDORSEMENT.

*** DETACH THIS STRIP FROM THE CHECK AT THE PERFORATIONS ABOVE THIS MESSAGE *** ...GE ***

QUESTIONS REGARDING PAYMENTS SHOULD BE DIRECTED TO: [redacted]

2053880 80

INVOICE DATE	INVOICE NUMBER	*	DISCOUNT TAKEN	NET AMOUNT	PO/REFERENCE	DESCRIPTION OF PAYMENT	...YMENT
06/17/05	0012418-IN			4,579.38	5-17928		
						00[redacted]01	
0252900-800 ENDOCARE						$4,579.38	

* CORRECTION CODES:

1) California State Sales or Use Tax deducted:
   a) Purchase is for resale in this instance. Permit number for the Irvine Campus is SR EA 24-141560.
   b) Title remains with the government.
2) California State Sales or Use Tax added. Purchase is not for resale.
3) Arithmetical error on invoice has been corrected.
4) Transportation charge has been deducted. Purchase order quoted FOB destination.
5) Transportation charge has been deducted. Copy of freight bill was not furnished as required by terms of purchase order. Reference purchase order number on copy of freight bill and submit for payment.
6) Other corrections. See attached.

...e order quoted

... freight bill was ...ler. Reference ... submit for paym...

ECK MBER: 2053880

User: KH1 / [redacted]

endocare
extending life everyday
201 Technology Dr. Irvine, CA. 92618

INVOICE

(#12)

201 Technology
Irvine, CA 92618
(949) 450-5400

INVOICE NUMBER: 0011842-IN
INVOICE DATE: 05/06/2005

ORDER NUMBER: 0011387
ORDER DATE: 05/06/2005
SALESPERSON: 0393
CUSTOMER NO: 00-[redacted]

[redacted]

[redacted]

CONFIRM TO:
[redacted]

CUSTOMER P.O.	SHIP VIA	F.O.B.	TERMS
9388	UPS RED	IRVINE	2% 10. Net 30 Davs

ITEM NO.	UNIT	ORDERED	SHIPPED	BACK ORD	PRICE	AMOUNT
CRYO-206-F PROCEDURE KIT 2.4MM PROBES	EACH	5 WHSE: 000	5	0	2,500.00	12,500.00
R2.4 CRYOPROBE, RENAL, 2.4MM	EACH	2 WHSE: 000	2	0	1,000.00	2,000.00
CRYO-46-F CRYOPROBE, 5MM	EACH	1 WHSE: 000	1	0	850.00	850.00

Ck. # 1618
5/16/05

Fax (866) 313-3636

Net Invoice:	15.350.00
Less Discount:	0.00
Freight:	266.84
Sales Tax:	0.00
Invoice Total:	**15,616.84**

1618

011842-IN 5/6/05 15,616.90 312.34 15,304.56

00-[redacted]

/12/05 1618 ENDOCARE 312.34 $15,304.56

[redacted]31

[redacted]
28-7174/3251

1618

	DATE	AMOUNT
1618	May 12, 2005	*******$15,304.56

Memo: 00-WAV001

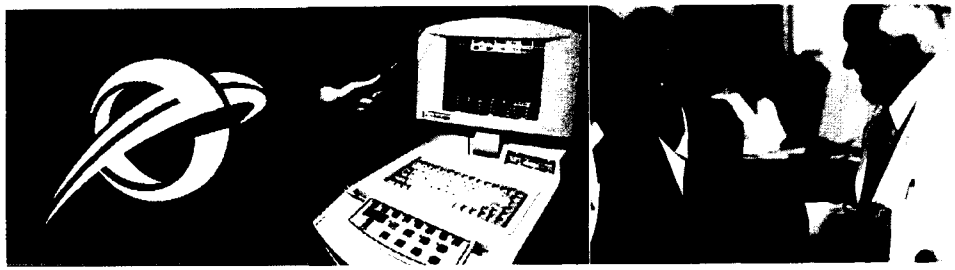
HE
ER

Fifteen Thousand Three Hundred Four and 56/100 Dollars

ENDOCARE
201 TECHNOLOGY
IRVINE, CA 92618

Security features. Details on back.

⑈001618⑈ ⑆325171740⑆ 5999179897 6⑈



CPT III Assignment to APC
Cryoablation of Renal Tumors

Centers for Medicaid and Medicare Services
December 14, 2005

Endocare
Mary Syiek, VP
Sharon Whalen, Sr. Director

Today's Agenda

- What is Percutaneous Renal Cryoablation
- New 2006 CPT III
- Assignment of Renal Cryoablation to APC
- Request to change APC Assignment

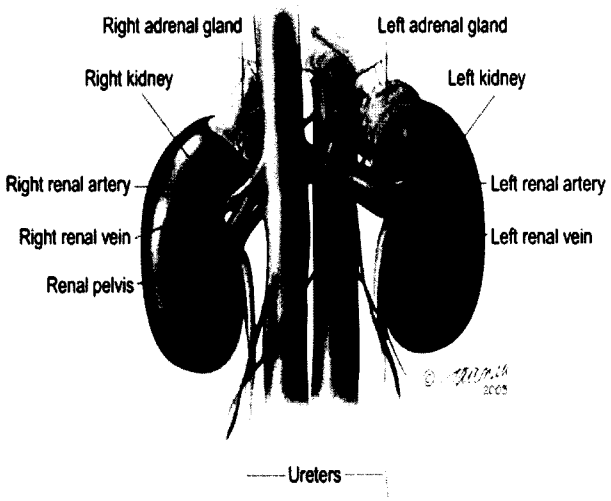
Renal Cancer

- Renal Cancer Incidence estimated to be 36,000 new cases in 2005

- 90% is Renal Cell Carcinoma (RCC)

- Renal Cancer presentation
  - Later stage (pain & hematuria)
  - Early stage – incidental finding due to increase use of diagnostics and improved imaging.

- RCC Treatment options: Surgical removal (partial or radial nephrectomy), ablation and surveillance.

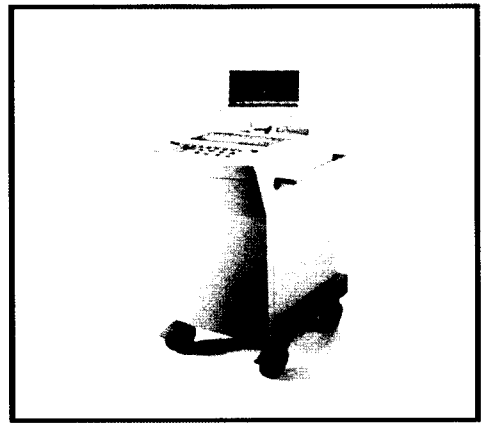


Ablation Treatment Option

- Ablation treatment goal = destroy a pre-determined volume of tissue either open, laparoscopically or percutaneously.
- Ablation is a minimally invasive treatment option & nephron-sparing.
- Nephron sparing surgery has emerged as a preferred option in the treatment of most renal tumors in patients with an existing or potential compromise of renal function and selected patients with a normal contra-lateral kidney.
- Cell death from cryoablation is caused by direct freezing, cell dehydration and ischemic hypoxia. The procedure generally involves two freeze and thaw cycles.

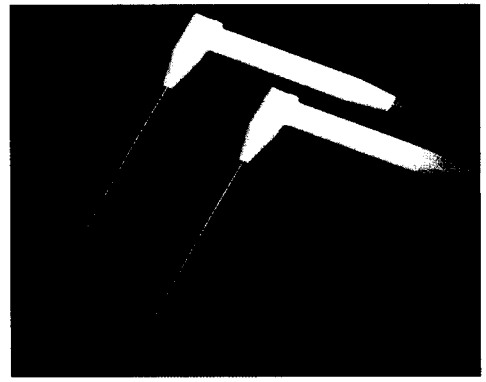
CRYO System

- Delivery of Argon gas to produce "Ice Ball"

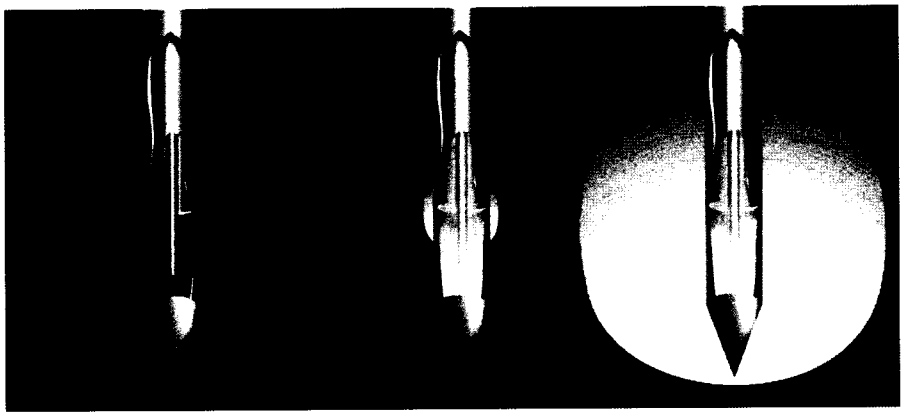


- Delivery of Helium for "thaw" phase

- Multiple Probe System (8 probes) and independently controlled

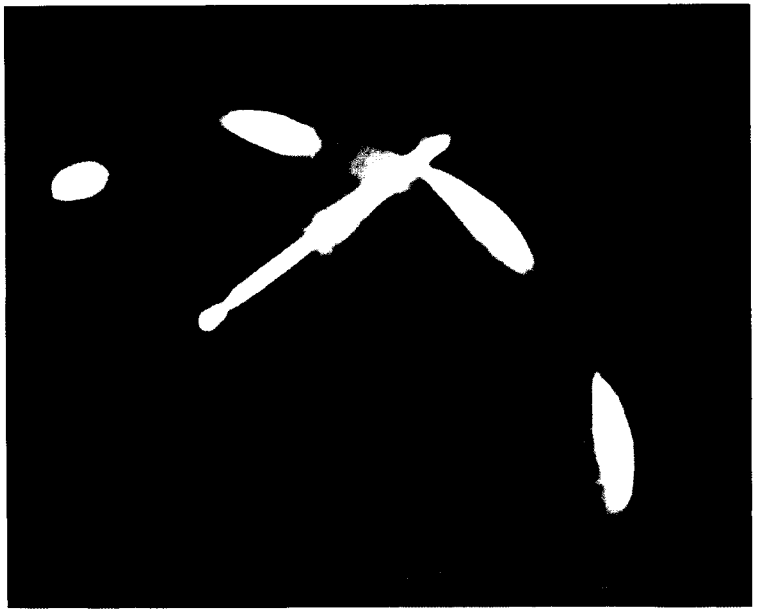


- CT-Compatible probes which fit within constraints of CT Gantry



How Does Cryoablation Work?

Able to monitor "Ice Ball" by CT Imaging



Cryoablation Clinical Efficacy - Laparoscopic

- Gill, (2005) from the Cleveland Clinic reported 3 year results :
  - 56 laparoscopic renal cryoablation patients
  - Mean tumor size was 2.3 cm
  - Tumor size reduction of 75% at 3 years and 38% had completely disappeared
  - Survival rate of 98%

Cryoablation Clinical Efficacy - Percutaneous

- Silverman (2005) 23 patients, mean tumor 2.6 cm, complete ablation in 92%, two complications (bleeding & abscess).

- Shingleton, (2003) 14 patients, mean tumor 3.1, 80% complete ablation, no complications.

- Shingleton (2001) 20 patients, mean tumor size 3.0, only one patient for re-treatment.

2006 New CPT III Code

- January, 2006 New CPT III Percutaneous Cryoablation, unilateral renal tumors
- AMA assigned as "new and emerging"
- Final 2006 Outpatient Rule assigned to APC 163 Level IV Cysto-Urethroscopy & Other GU procedures
- APC 163 Average payment ~$1,999

Request to change APC assignment

- Identification of more clinically and financially aligned APC
- CPT III is new & emerging and may be more appropriately aligned to New Technology APC.
- Other Options to consider:
  - 50592 - Percutaneous Renal Ablation for renal tumors, Radio-Frequency assigned to APC 423 Level III Perc Abdominal & Billiary Procedure

Practice Patterns

- Current Percutaneous Cryoablation for Renal Tumors is performed utilizing a CT monitoring system, occasionally ultrasound for probe placement

- Typical case positions cryo probe and ice ball formation around tumor to effectively freeze entire area versus one probe only.

- Average of 2.5 cryoablation probes.

- Conscious sedation / or general anesthesia

Cost of Percutaneous Cryoablation Renal Tumors

- Probe Expense to Hospital
  - ~$1000 per probe (see invoices/cancelled checks provided)
  - Average probe use for percutaneous renal cryoablation is 2.3 probes (Dr. Peter Littrup, Karmonos Cancer Institute, 2005)
- Hospital Costs
  - Mayo Clinic estimates costs to be ~$9,100 (for 1.23 days).
  - Dr. Steve Solomon at Johns Hopkins presented costs at RSNA of $3,000 for the outpatient procedure.

Other APC Options

CPT	Description	APC	Payment
50592	Percutaneous Renal Ablation for renal, Radio-Frequency	**423** - Level III Perc Abdominal & Billiary Procedure	**$2355**
		1524 - New Technology XIV	**$3,250**

In Summary

- Current procedure costs in $3,000 to $9,000 range.
- On average 2.5 cryoprobes are used for renal cryoablation; average probe purchase price is ~$1000/probe.
- Costs of cryoprobes alone exceed the total APC 163 payment of ~$1,999.
- Request made for CMS to move the CPT III 0135 T to a more clinically and financially aligned APC such as APC 423; or assign to a New Technology APC that provides sufficient payment to cover hospital costs.
- This change will ensure that this new technology is not discriminated against in favor of more costly inpatient procedures.

Thank You

26

Coalition For The Advancement Of Brachytherapy

660 Pennsylvania Avenue, S.E.
Suite 201
Washington, D.C. 20003
(202) 548-2307
Fax: (202) 547-4658

September 25, 2006

Via Overnight Delivery

The Honorable Mark McClellan, M.D., Ph.D.
Administrator
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Attention: CMS-1506-P
Mail Stop C4-26-05
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: CMS-1506-P Medicare Program; Hospital Outpatient Prospective Payment System and CY 2007 Payment Rates; Proposed Rule – Brachytherapy – Letter 1 of 2

Dear Dr. McClellan:

The Coalition for the Advancement of Brachytherapy (CAB) is pleased to submit comments to the Centers for Medicare and Medicaid Services (CMS) in response to the August 23, 2006 Hospital Outpatient Prospective Payment System (HOPPS) Proposed Rule.

Please note that CAB will submit two (2) separate comment letters regarding the HOPPS proposed rule for your consideration. A second letter, to be sent under separate cover, will specifically address the proposed payment methodology for brachytherapy sources in 2007 and CAB's rationale for recommending continuation of the current payment methodology of hospital charges reduced to costs. This comment letter will address all of CAB's other comments involving the August 23rd HOPPS proposed rule.

CAB was organized in 2001 and is composed of the leading developers, manufacturers, and suppliers of brachytherapy devices, sources, and supplies. CAB's mission is to work for improved patient care by assisting federal and state agencies in developing reimbursement and regulatory policies to accurately reflect the important clinical benefits of brachytherapy. Such reimbursement policies will support high quality and cost-effective care. Over 90% of brachytherapy procedures performed in the United States are done with products developed by CAB members and it is our mission to work for improved care for patients with cancer (see Attachment 1).

We would like to thank CMS for the opportunity to meet with staff during the past several years to explore how refinements can be made for brachytherapy payment and coding under HOPPS. Although CMS has made significant changes in brachytherapy payment policy, the Medicare Modernization Act and CMS' recent proposed rule highlight that further refinements are essential to ensure appropriate payment to hospitals and meaningful access to high quality cancer treatment for Medicare patients.

The following recommendations, which are discussed in detail in subsequent sections of this letter, build upon the recent meetings between CMS and CAB on May 1, 2006 and September 18, 2006.

CAB's Primary Recommendation:

CMS should continue the current payment methodology for brachytherapy devices in the hospital outpatient setting (hospital's charges adjusted to cost for each device provided on a patient-by-patient basis) for all brachytherapy devices in 2007 and 2008. This issue will be addressed in detail in a separate CAB comment letter to be sent under separate cover.

CAB's Additional Recommendations:

- CMS should establish two new HCPCS codes for stranded Iodine-125 and stranded Palladium-103 sources in 2007.
- CMS should revise the proposed definition of brachytherapy sources to include all brachytherapy sources, without limitation. Further, CMS should establish a new brachytherapy source HCPCS code for electronic brachytherapy effective January 1, 2007.
- CMS should maintain breast brachytherapy codes 19296 and 19297 in their current New Technology APCs (1524 and 1523 respectively) for 2007. Alternatively, CMS could assign CPT codes 19296 and 19297 to clinical APC 648 Breast Reconstruction with Prosthesis. To appropriately capture all procedures in APC 648, it is also recommended that CMS revise the APC group title from "Breast Reconstruction with Prosthesis" to "Level IV Breast Surgery."
- CMS should continue to require hospitals to report the use of HDR Iridium-192 sources (C1717) per fraction.
- CMS should adopt Option 1 proposed by CMS and reimburse Ytterbium-169 (C2637) at charges adjusted to cost, consistent with the payment methodology that should be used for all brachytherapy sources.
- CMS should use the current payment policy (hospital's charges adjusted to cost) for new or established brachytherapy sources when no hospital claims-based data is available.
- CMS should include in the HOPPS final rule or the January 2007 HOPPS Medicare Program Transmittal clarification that the policy of billing all types of brachytherapy sources actually prescribed and ordered remains in force, notwithstanding the reference to "used" in the December 19, 2003 Program Transmittal.
- CMS should implement mandatory code edits for brachytherapy procedure APCs 312, 313 and 651.
- APC relative weights should be based on appropriate claims.

I. OPPS BRACHYTHERAPY-NEW BRACHYTHERAPY SOURCE CODES

CMS should establish two new HCPCS codes for stranded Iodine-125 and stranded Palladium-103 sources in 2007.

Significant concerns about the adequacy of CMS' data on brachytherapy devices were at the core of Congress' decision to enact Section 621(b) of the MMA in 2003. Similarly, ongoing concerns regarding CMS' data resulted in very recent recommendations from two Congressionally-created expert Advisory Panels to continue the current reimbursement methodology for brachytherapy devices.

As Congress highlighted in the MMA, one critical step in resolving these data problems is to ensure that CMS creates and uses separate codes for brachytherapy devices that reflect clinically-relevant distinctions among different types of brachytherapy devices. These codes should evolve over time.

However, CMS' current 2005 data does not reflect the important new clinical protocols that have emerged over the last decade resulting in increased clinical use of "stranded" brachytherapy devices for the treatment of prostate cancer. Stranded brachytherapy sources are embedded into the stranded suture material (such as polyglactin) and separated within the strand by material of an absorbable nature at specified intervals. This ensures the initial and long-term position of each source when implanted in and around cancerous tumors. This special stranded source is manufactured prior to delivery to the customer and is not a process which can be performed by a hospital.

In reviewing the age of the data used in the GAO's survey, the GAO noted that one brachytherapy professional society recommended that the data used to establish reimbursement rates should reflect the increased clinical use of stranded brachytherapy devices. The society highlighted that stranded brachytherapy devices are "more costly but considered clinically advantageous."[1] These observations underscore the need for new codes for stranded Iodine-125 and Palladium-103 sources.

Stranded sources are distinct from traditional brachytherapy devices in a number of fundamental ways, including the following (see attachments 2-5):

- As demonstrated in the clinical literature and widespread clinical practice, stranded sources improve patient safety and clinical outcomes in the treatment of prostate cancer.
- The radioactive intensities required for stranded Iodine-125 or Palladium-103 brachytherapy sources are greater than traditional loose sources utilized to treat prostate cancer.
- Stranded Iodine-125 and Palladium-103 sources have increased costs of production arising from a number of factors, including the cost of using increased radioactivity due to the additional preparation time, along with the material and labor costs associated with "stranding" the sources with spacing that is consistent with the treating physician's specific prescription for a particular patient.
- Stranded Iodine-125 and Palladium-103 sources require separate FDA clearances from traditional Iodine-125 and Palladium-103 sources.

Stranded sources can be placed at the periphery of the prostate or outside the prostate gland, permitting treatment of extra-prostatic extension of the disease without the potential for migration

---

[1] U.S. Gov't Accountability Office, *Rates for Certain Radioactive Sources Used in Brachytherapy Could Be Set Prospectively* (GAO-06-635, July 2006).

service (or group of services)." Under this section, current cancer therapy drugs and biologicals and brachytherapy are defined as follows:

> "A drug or biological that is used in cancer therapy, including (but not limited to) a chemotherapeutic agent, an antiemetic, a hematopoietic growth factor, a colony stimulating factor, a biological response modifier, a bisphosphonate, and device of brachytherapy..."

The above definition does not require that a device of brachytherapy consist of "a seed or seeds (or radioactive source)" as proposed by CMS. Furthermore, the definition clearly states "but not limited to," therefore the list of drugs and biologicals is not exclusionary and is meant to be inclusive of all drugs and biologicals used in cancer therapy.

The evolution of technology requires one to reexamine existing assumptions, understandings, and definitions once thought to be clear and defined. One of these assumptions is that brachytherapy sources have to be radioactive to deliver a therapeutic radiation dose. Technological advances demonstrate that non-radioactive (electronic) sources, for example, can deliver a therapeutic radiation dose similar to a radioactive source or seed.

Brachytherapy is derived from ancient Greek words for short distance (brachy) and treatment (therapy). The procedure is most often an outpatient procedure used in the treatment of different kinds of cancer. Brachytherapy sources are carefully placed inside of the cancerous tissue and positioned in a manner that will attack the cancer most efficiently. In the treatment of cancer using brachytherapy, sources give off radiation that travels only a few millimeters to kill nearby cancer cells. Brachytherapy treatment does not define the type of source; brachytherapy is the type of treatment the patient receives whereas many different types of sources, radioactive and non-radioactive may be appropriate.

CAB's understanding is that MMA legislation ensures separate payment for all devices of brachytherapy. The MMA does not exclude any specific devices, but rather requires CMS to better define and categorize those devices. New innovative, non-radioactive brachytherapy sources meet the criteria required by the legislation and are approved as brachytherapy devices by the Food and Drug Administration (FDA). By narrowing the definition of a brachytherapy source to a radioactive source only, CMS would not only limit access to new technology, but also inadvertently eliminate Medicare beneficiary access to FDA-approved cancer care.

CAB does not support the CMS proposed definition of a brachytherapy source. Further, CMS should establish a new brachytherapy source HCPCS code for electronic brachytherapy effective January 1, 2007:

> C26XX Brachytherapy device, High Dose Rate X-Ray Radiation, per source

III. OTHER NEW TECHNOLOGY APCs

CMS should maintain breast brachytherapy codes 19296 and 19297 in their current New Technology APCs (1524 and 1523 respectively) for 2007. Alternatively, CMS could assign CPT codes 19296 and 19297 to clinical APC 648 Breast Reconstruction with Prosthesis. To appropriately capture all procedures in APC 648, it is also recommended that CMS revise the APC group title from "Breast Reconstruction with Prosthesis" to "Level IV Breast Surgery."

Breast brachytherapy codes (CPT 19296, 19297 & 19298) were implemented on January 1, 2005 and have been assigned to New Technology APCs since 2005. CMS proposes to reassign two of the three

codes from New Technology APCs to clinical APCs in 2007. The CMS proposed APC assignment would result in significant decreases in 2007 payment, which ranges from –22.8 to –37.0 percent (see Table 1). If CMS finalizes the proposed clinical APC assignment, this will limit the breast surgeon's and radiation oncologist's ability to offer breast brachytherapy as a cancer treatment option to Medicare eligible women because hospitals would not likely purchase the breast brachytherapy catheter since the cost of the device exceeds the proposed APC payment rate. Therefore the CMS proposed payment reduction will limit patient access to this less invasive breast cancer treatment.

Table 1

HCPCS Code	2006 APC	2006 Payment	2007 Proposed APC	2007 Proposed Payment	Payment Change 2006-2007	Percentage Change 2006-2007
19296 Breast interstitial radiation treatment, delayed	1524	$3,250.00	30	$2,508.17	($741.83)	**-22.8%**
19297 Breast interstitial radiation treatment, immediate	1523	$2,750.00	29	$1,732.69	($1,017.31)	**-37.0%**

The HOPPS relative weights for 2007 are based on hospital claims data from January 1-December 31, 2005. CPT Codes 19296 and 19297 were new codes in 2005 and CMS is relying solely on calendar year 2005 hospital claims data to set 2007 payment rates. The number of hospital outpatient claims is low and inadequate for CMS to make assumptions regarding which clinical APC to assign these codes (see Table 2). Further, the volume of procedures in 2005 for CPT codes 19296 and 19297 were low in comparison to other device-dependent procedures. CMS should maintain 19296 and 19297 in New Technology APCs 1524 and 1523 respectively, so that the agency may collect claims data through calendar year 2006 and reevaluate reassignment to a more appropriate clinical APC for 2008.

Table 2

CPT code	2004 Claims Used to Determine 2006 Payment (number of single frequency claims)	2005 Claims Used to Determine 2007 Payment (number of single frequency claims)
19296	n/a	491
19297	n/a	36
19298	n/a	49

Breast brachytherapy CPT codes 19296, 19297 and 19298 require the use of a high cost device that is bundled into the procedure payment thus classifying these procedures as device-dependent. CPT 19296 and 19297 are similar both clinically and with respect to resource costs to procedures included in APC 648 Breast Reconstruction with Prosthesis. All of the procedures in APC 648 involve the placement of an expensive device, as do breast brachytherapy codes 19296 and 19297.

As an alternative, CMS could assign CPT codes 19296 and 19297 to APC 648 Breast Reconstruction with Prosthesis. The identical medical device is required for both breast brachytherapy procedures (CPT 19296 and 19297) and the cost of the catheter is exactly the same. Further, the cost of the device required for APC 648 Breast Reconstruction with Prosthesis is similar to the breast catheter required for CPT 19296 and 19297.

IV. OPPS BRACHYTHERAPY-HIGH DOSE RATE IRIDIUM-192 (C1717)

CMS should continue to require hospitals to report the use of HDR Iridium-192 source (C1717) per fraction.

CMS invites comment on alternative payment methodologies for the reusable High Dose Rate (HDR) Iridium-192 Brachytherapy Source (C1717).

CAB strongly supports separate payment for the HDR Iridium-192 source as is required under the MMA, but CAB is concerned that the proposed 2007 payment of $134.93 per fraction provides an inadequate payment, especially for hospitals that do not provide a high volume of HDR brachytherapy.

Iridium-192 is a reusable source with cost allocated among the number of patients treated, typically during a 90 day period.

Iridium-192 source is required per patient treatment and treatment protocols may vary from two treatments per day to one treatment per week. Due to the significant treatment variations among patient protocols, payment for Iridium-192 should remain on a per treatment basis and not be changed to per treatment day. Continued changes in hospital reporting requirements will confuse providers and will lead to inconsistency in claims data making future payment rates unstable.

V. OPPS BRACHYTHERAPY-YTTERBIUM-169 (C2637)

CMS should adopt Option 1 proposed by CMS and reimburse Ytterbium-169 (C2637) at charges adjusted to cost, consistent with the payment methodology that should be used for all brachytherapy sources.

Ytterbium-169 is a High Dose Rate brachytherapy source and has been approved by the Food and Drug Administration (FDA). It is our understanding that the manufacturer of this medical device submitted an application and supporting materials to obtain a brachytherapy source code (i.e. C2637) following FDA approval in 2005. This source will be available in 2007 and we understand that CMS does not have hospital claims data for Ytterbium-169.

CMS considered four (4) options in establishing payment for Ytterbium-169. CMS proposed to assign Ytterbium-169 (C2637) to its own APC with a payment rate set at or near the lowest proposed payment rate for any brachytherapy source paid on a per source basis (Option 2).

Ytterbium-169 is a High Dose Rate (HDR) source with unique characteristics and differences in application than other sources. Ytterbium-169 (C2637) has a shorter half-life than HDR Iridium-192 (C1717) and requires source replacement every 32 days vs. 90 days for HDR Iridium-192. In addition, Ytterbium-169 requires different shielding and has a unique target activity compared to HDR Iridium-192.

Since there are no other sources that are comparable to this new brachytherapy source, the most appropriate payment methodology for Ytterbium-169, and any new brachytherapy source, would be to use the "charges adjusted to costs" methodology for a minimum of two years while CMS collects hospital claims data to establish payment values. This option would be similar to the CMS policy for New Technology APCs.

VI. OPPS BRACHYTHERAPY-PAYMENT FOR NEW BRACHYTHERAPY SOURCES

CMS should use the current payment policy (hospital's charges adjusted to cost) for new or established brachytherapy sources when no hospital claims-based data is available.

CMS seeks public comment regarding setting payment amounts for established or new brachytherapy sources eligible for separate payment when no hospital claims-based cost data is available. CAB recommends that CMS continue their current payment policy of hospital charges reduced to cost for new or established brachytherapy sources when no hospital claims-based cost data is available.

VII. OPPS BRACHYTHERAPY-HOSPITAL BILLING CLARIFICATION REGARDING BRACHYTHERAPY SOURCES

CMS should include in the HOPPS final rule or the January 2007 HOPPS Medicare Program Transmittal clarification that the policy of billing all types of brachytherapy sources actually prescribed and ordered remains in force, notwithstanding the reference to "used" in the December 19, 2003 Program Transmittal.

A December 19, 2003 Medicare Program Transmittal (Transmittal 32, Change Request 3007, Publication 100-20) appeared to instruct hospitals to bill for prostate brachytherapy sources used, while prior CMS policy has made clear that hospitals can bill for sources that the physician has actually ordered.

Specifically, in the fall of 2001, CMS (then HCFA) issued on its Medlearn website Frequently Asked Questions, including the following:

> **Q. 114** Can hospitals bill for all brachytherapy seeds ordered by the physician even if the physician does not use all of the brachytherapy seeds?
>
> **A. 114** Yes. There may be times when a physician orders more brachytherapy seeds than necessary since the physician may not know the exact amount of brachytherapy seeds needed for one patient. In this case, the hospital may bill for all of the brachytherapy seeds ordered.

We agree with this clarification. In fact, ASTRO has a coding corner Q & A guidance for its members (see http://www.astro.org/healthcare_economics/coding_corner/brachyseeds.htm) which states:

CODING QUESTION: An ASTRO member attended the 2004 ASTRO Socioeconomic Lunch and has the following question:

> For prostate seed implants, the member typically orders 6 extra seeds in addition to the preplan count. There was an ACR Bulletin back in December 2001 that said, "Therefore, it is valid that the hospital charge the "ordered seed" inventory for each patient, accounting for the seeds ordered only once." Is that still true? Should they bill for the number of seeds ordered or the number of seeds implanted in 2005?
>
> "The ASTRO Code Utilization and Application Subcommittee (CUAS) is not aware of anything that has changed in 2005 on this issue. It is presumed in the ACR statement on the seed inventory, that these extra seeds are either used, returned, or wasted--never transferred to another patient. Thus, it is appropriate for all seeds to be charged for, not just the ones that the doctor uses."

CAB was concerned when CMS issued the January 2004 Hospital Outpatient Prospective Payment System Update that it could be misconstrued to restrict hospitals to only bill for seeds actually used (see section below which is underscored from December 19, 2003 Medicare Program Transmittal 32):

> January 2004 Update of the Hospital Outpatient Prospective Payment System (OPPS)
>
> "7. Payment for Prostate Brachytherapy In 2003, CMS paid a packaged amount for prostate brachytherapy. Hospitals were required to bill using HCPCS code G0256 (prostate brachytherapy with palladium sources), when palladium sources were implanted, and HCPCS code G0261 (prostate brachytherapy with iodine sources). These HCPCS codes were to be used in lieu of separate billing for CPT codes 77778 (interstitial radiation source application; complex) and 55859 (transperineal placement of needles or catheters into prostate for interstitial radiation element application, with or without cystoscopy), and HCPCS codes C1718 (iodine sources) and C1720 (palladium sources).
>
> Under the OPPS for 2004, HCPCS codes G0256 and G0261 are deleted. For services furnished on or after January 1, 2004, hospitals are to use the CPT codes 77778 and 55859 to bill for the procedures and HCPCS codes C1718 and C1720 to bill for the brachytherapy sources. Separate payments will be made for the procedures and for the sources. Hospitals are to bill the brachytherapy sources showing the number of sources used in the units column. For example, if 100 brachytherapy sources are implanted in the prostate, the hospital will bill 100 units of the applicable code for the brachytherapy source."

This final section could be misconstrued by hospitals to limit billing to only prostate brachytherapy sources used, even if the physician prescribed in good faith what he/she believed to be necessary for the clinical needs of the patient, and the hospital, following the physician's prescription, purchased the prescribed number of sources. It is not uncommon for a treatment plan to be modified slightly in the operating room on the day of the implant. Physicians typically order extra sources for implant procedures so if the treatment plan must be altered during the course of treatment, or the physician determines a few extra sources are necessary to treat the patient, the additional sources are available to implant at the time of the procedure. In most cases, all ordered seeds are implanted leaving few that are left to decay. In either case, the hospital is required to absorb the cost of all the seeds ordered. Hospitals should not be penalized for following a physician's prescriptive order.

CAB has sent formal correspondence to CMS on three separate occasions (April 27, 2005 to Don Thompson; May 20, 2004 to Cindy Read; and September 19, 2005 to Jim Hart) and requested clarification of this CMS policy in the hospital outpatient setting (see attachments 9-11). To date, we have not received a response from CMS to our letters or follow up emails regarding this issue.

VIII. DEVICE-DEPENDENT APCS-MANDATORY CODE EDITS

CMS should implement mandatory code edits for brachytherapy procedure APCs 312, 313 and 651.

CAB continues to support mandatory reporting of all medical device "C" codes and related incentives to encourage hospitals to be more vigilant in reporting the total costs of performing device-related services. We recommend that CMS consider expanding their proposal to implement device code edits for all device-related and "device-dependent" APCs. Furthermore, we encourage CMS to accelerate its efforts to educate hospitals on the importance of accurate coding for devices and other technologies. At the

APC Advisory Panel meeting on August 24 2006, the American Hospital Association (AHA), the Provider Round Table group and the APC Advisory Panel members who have oversight for coding agreed that requiring the appropriate device on the claim prior to processing and paying the claim was very helpful to the hospitals in terms of educating them on the appropriate device C-Codes that should be required for procedures, particularly the more complex procedures.

Brachytherapy requires the use of medical devices and we suggest that brachytherapy source "C" codes be required for APCs 312, 313, and 651. We believe that limited mandatory "C" coding will be more of an administrative burden to hospitals and may cause confusion. We support expanding the 2007 policy to all device-related and "device-dependent" APCs to promote "correct coding" and to improve the quality of the claims data. In addition to using device "C" codes, hospitals should be educated on how to report charges for brachytherapy source devices utilized in the outpatient department.

IX. APC RELATIVE WEIGHTS

CAB appreciates the agency's efforts to include multiple procedure claims data to calculate relative payment weights by using the "same date of service" and an expanded list of "bypass" codes to provide more single and "pseudo" single claims, however, the continued reliance on single procedure claims fails to produce a statistically valid number and sample of brachytherapy procedure claims used for rate-setting. Additional revisions to the current methodology must be explored to ensure that CMS is basing payment on a substantial number of accurate hospital claims.

CONCLUSION

Brachytherapy offers important, clinically effective cancer therapies to Medicare beneficiaries. Appropriate payment for brachytherapy procedures and sources is necessary to ensure that Medicare beneficiaries will continue to have full access to high quality cancer treatment in the hospital outpatient setting.

We hope that CMS will take these issues under consideration during the development of the 2007 Hospital Outpatient Final Rule. Should CMS staff have additional questions, please contact Gordon Schatz, Esq. at (202) 414-9259 or Wendy Smith Fuss, MPH at (703) 534-7979.

Thank you for your consideration.

Sincerely,

Lisa Hayden
Chair

Janet Zeman
Vice-Chair

cc: Carol M. Bazell, M.D.

ATTACHMENTS

1. CAB Member Companies and Advisory Board

2. Lee, William Robert et al. "Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy." Radiotherapy and Oncology 65 (2002): 123-127

3. Al-Qaisieh, Bashar et al. The use of linked seeds eliminates lung embolization following permanent seed implantation for prostate cancer. Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, pp. 397-399, 2004

4. Eshleman, MD, Jeffrey S. et al. Radioactive seed migration to the chest after transperineal interstitial prostate brachytherapy: extraprostatic seed placement correlates with migration. Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, pp. 419-425, 2004

5. Fagundes, Humberto M. et al. Transperineal TRUS-guided prostate brachytherapy using loose seeds versus RAPIDStrand: A dosimetric analysis. Brachytherapy 3 (2004) 136-140

6. Rivard, Mark J et al. Calculated and measured brachytherapy dosimetry parameters in water for the Xoft AXXENT S-Ray source: An electronic brachytherapy source.

7. Kraus-Tiefenbacher, Uta et al. Long-term toxicity of an intraoperative radiotherapy boost using low energy x-rays during breast-conserving surgery. Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 2, pp. 377-381, 2006

8. Vaidya, J.S. et al. Targeted intra-operative radiotherapy (Targit): An innovative method of treatment for early breast cancer. Annals of Oncology 12:1075-1080, 2001

9. April 27, 2005 Letter to Don Thompson

10. May 20, 2004 Letter to Cindy Read

11. September 19, 2005 Letter to Jim Hart

ATTACHMENT 1

Attachment 1

Coalition for the Advancement of Brachytherapy (CAB)

The Coalition for the Advancement of Brachytherapy (CAB) is a national non-profit association composed of manufacturers and developers of sources, needles and other brachytherapy devices and ancillary products used in the fields of medicine and life sciences. CAB members have dedicated significant resources to the research, development and clinical use of brachytherapy, including the treatment of prostate cancer and other types of cancers as well as vascular disease. Over 90% of brachytherapy procedures performed in the United States are done with products developed by CAB members.

Member Companies

BrachySciences
C.R. Bard, Inc.
Cytyc Corporation
IsoRay
MDS Nordion
Mentor Corporation
Nucletron Corporation
Oncura
SIRTeX Medical, Inc.
Theragenics Corporation
Varian Medical Systems
Xoft, Inc.

CAB Advisory Board

American Brachytherapy Society
American College of Radiation Oncology
Association for Freestanding Radiation Oncology Centers
Society for Radiation Oncology Administrators

ATTACHMENT 2

ELSEVIER

Radiotherapy and Oncology 65 (2002) 123–127

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy

William Robert Lee[a,*], Allan F. deGuzman[a], Shannon K. Tomlinson[a], David L. McCullough[b]

[a]*Department of Radiation Oncology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1030, USA*
[b]*Department of Urology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1030, USA*

Received 23 November 2001; received in revised form 13 September 2002; accepted 27 September 2002

Abstract

Background and purpose: Reports using the retropubic and transperineal technique of prostate brachytherapy suggest that adequate radiation doses are required for good clinical results with I-125. After 3 years of using loose sources (LS), radioactive sources embedded in suture (SES) were introduced into our prostate brachytherapy technique. The purpose of the present report is to determine whether dosimetric quantifiers of implant adequacy were affected by the use of SES.

Materials and methods: Between September 1999 and April 2000, 20 patients were treated with prostate brachytherapy alone with a preplanned, preloaded needle technique using LS. Between May 2000 and February 2001, 20 patients were treated with prostate brachytherapy alone with a preplanned, preloaded needle technique using SES. Dosimetric quantifiers (DQ) of implant adequacy were calculated using a computed tomography scan performed 1 month following prostate brachytherapy. DQ were compared between patients treated with LS and patients treated with SES.

Results: The demographic characteristics were similar for each group. Men treated with SES had slightly smaller prostate glands compared to men treated with LS. The mean total activity and activity per seed were similar for each group but the activity per unit volume was slightly higher for the SES group. Patients treated with SES were found to have significantly improved DQ compared to patients treated with LS. The mean V100 for patients treated with SES was 94.10% compared to 86.54% in those patients treated with LS ($P < 0.001$).

Conclusions: In our experience using preplanning and preloaded needles, the use of SES is associated with improved postimplant DQ.

Keywords: Prostate cancer; Interstitial brachytherapy; Iodine 125

1. Introduction

Prostate cancer is the most commonly diagnosed solid tumor in American men. In 2001, approximately 198 100 new cases will be diagnosed [10]. A majority of these cases will be clinically organ confined at the time of diagnosis [10]. The management of organ-confined adenocarcinoma of the prostate remains one of the most controversial areas in all of oncology. Treatment options include expectant management, radical prostatectomy, external beam radiation therapy, and interstitial brachytherapy [2]. In the absence of prospective randomized trials, proponents of each technique continue to aver that one therapy is superior to all others.

Prostate brachytherapy (PB) has been used for many decades with heterogeneous results [6,8,15,22]. Improvements in technology have allowed the development of a transperineal approach in which radioactive sources can be placed accurately within the prostate gland using real time ultrasound guidance [6]. Excellent results have been reported with the use of brachytherapy alone in men with favorable risk disease, and brachytherapy combined with external beam radiation therapy in men with intermediate risk prostate cancer [6,7,8,15].

With the development of sophisticated treatment planning systems, it is now possible to obtain three-dimensional dosimetric evaluations soon after PB is completed [5,13]. The American Brachytherapy Society has recommended that all patients treated with PB undergo some form of dosimetric analysis following treatment [13]. This is most commonly achieved with a pelvic computed tomography (CT) scan performed within weeks after prostate brachytherapy. A number of dosimetric quantifiers (DQ) have been studied and reported. The two DQ that have been most closely studied include V100 and D90 [13,18–20]. V100 represents the percentage of the prostate volume

* Corresponding author.

0167-8140/02/$ - see front matter
PII: S0167-8140(02)00305-5

that receives 100% of the prescription dose. D90 is the maximum dose received by 90% of the prostate gland.

A seminal report from the largest reported series using retropubic seed placement observed that the prescription dose often was not achieved because of inaccurate seed placement [9]. Importantly in this report, lower prostate doses were associated with inferior outcomes, especially local relapse. The few patients that received homogeneous high doses to the prostate gland achieved excellent local control rates.

A recent report of patients treated with a modern transperineal ultrasound-guided technique also reports a dose response relationship [20]. In this series all patients underwent postimplant dosimetric analysis using CT scans obtained approximately 1 month following prostate brachytherapy. Those patients found to have a D90 of greater than 140 Gy experienced improved disease-free survival when compared to patients found to have a D90 of less than 140 Gy. This data with modern technique supports the notion that disease control is associated with dosimetric parameters that can be easily measured. A technique that increases the likelihood of achieving adequate radiation dose of the prostate gland should result in improved disease control.

Although many different techniques are utilized during prostate brachytherapy, most patients are treated with loose sources (LS). A unique medical device that consists of loose seeds embedded in stiffened suture has been developed (RAPIDStrand™, Nycomed Amersham, United Kingdom). This formulation allows for the placement of sources outside of the prostate gland without the concern of seed migration that has been documented with loose seeds [21]. The fixed geometric distribution of seeds embedded in suture (SES) reduces spacing errors and may allow for improved dose delivery [16].

After approximately 3 years of performing prostate brachytherapy at Wake Forest University using LS, we incorporated SES into the prostate brachytherapy procedure. The purpose of this analysis is to determine if the use of SES is associated with improved DQ compared to the use of LS.

2. Materials and methods

2.1. Brachytherapy technique

Transperineal prostate brachytherapy at Wake Forest University began in September 1997. The technique has been previously described by Blasko and Grimm [6]. This technique relies on preplanning using an ultrasound volume study of the prostate gland. Based on the preplan sources are ordered and preloaded into brachytherapy needles using catgut spacers to ensure adequate spacing between sources. From September 1997 until April 2000, all men were treated with LS. In May of 2000, SES were incorporated into the brachytherapy procedure. The needles containing SES were confined to the periphery of the prostate gland. LS were utilized in the center of the prostate gland. On average for a SES implant, 70–80% of the sources were SES. This technique differs from that of Batterman and others where SES are used throughout the gland [4]. All patients were treated with I-125 alone and the prescription dose was 144 Gy.

2.2. Dosimetric evaluation

According to a uniform institutional protocol, 1 month following prostate brachytherapy, all men underwent a CT scan of the pelvis and prostate. Three millimeter thick images were obtained at 3 mm scan intervals from 2 cm above the most superior seed to 2 cm below the most inferior seeds. The images were then transferred by local area network to the Treatment Planning System. Prostate volumes were outlined by single radiation oncologist (WRL). A single physicist localized each individual seed on the CT scan, and isodose volumes were calculated. Dose volume histograms were calculated with 0.5 mm pixel spacing, the voxel size was 1.25 cc and the dose bins were 5 Gy. A variety of DQ were examined to allow comparison between the patients treated with LS and those treated with SES. At the recommendation of the American Brachytherapy Society, we have reported the V100 and D90 [13]. The rate of seed migration was determined by a KUB film and chest X-ray taken 1 month following the implant procedure.

2.3. Statistical analysis

Descriptive analyzes were performed using PCSAS Version 6.12. Comparison of categorical variables relied on the chi-square test and continuous variables were compared using the t-test. The assumptions of these tests were met and no transformations were required. All P values are two-sided.

3. Results

The patient and treatment characteristics for the entire study population are listed in Table 1. The characteristics are also sorted according to implant technique (LS versus SES). None of the demographic characteristics are significantly different between the LS and SES groups. Men treated with SES did have slightly smaller prostate glands on average than men treated with LS (SES 33.74 cc, LS 39.55 cc; $P = 0.0474$). The treatment parameters were similar for each group although the SES group did have a significantly higher activity per unit volume of prostate (LS 0.92 mCi/cc, SES 1.02 mCi/cc, $P = 0.0091$). Seed migration was observed in two (10%) patients treated with LS. Seed migration was not seen in any patients treated with SES.

Table 2 lists the dosimetric quantifiers of implant

Table 1
Patient and treatment characteristics of the overall study population ($n = 40$) and stratified by implant technique[a]

Variable	Overall ($n = 40$)	LS group ($n = 20$)	SES group ($n = 20$)	P-value
Mean age (SD)	65.8 (5.4)	66.65 (5.3)	65 (5.6)	NS
T1 (%)	29 (72)	14 (70)	15 (75)	NS
T2 (%)	11 (28)	6 (30)	5 (25)	
Mean pPSA (ng/ml)	6.44	6.43	6.44	NS
Gleason 2–6 (%)	37 (92)	18 (90)	19 (95)	NS
Gleason 7 (%)	3 (8)	2 (10)	1 (5)	
Mean (SD) prostate volume (cc)	36.6 (9.3)	39.55 (10.7)	33.74 (6.9)	0.0474
Mean (SD) activity/source (mCi)	0.36 (0.03)	0.35 (0.02)	0.36 (0.03)	NS
Mean (SD) total activity (mCi)	34.77 (6.0)	35.16 (5.88)	34.39 (6.3)	NS
Mean (SD) activity/volume (mCi/cc)	0.97 (0.14)	0.92 (0.14)	1.02 (0.11)	0.0091

[a] SD, standard deviation; NS, not significant; and $P > 0.05$.

adequacy for the entire group and stratified by implant technique. By any measure, those patients treated with SES were found to have significantly improved dosimetric coverage of the prostate gland. The mean V100 for those patients treated with SES was 94.10 versus 86.54% in those patients treated with LS ($P < 0.001$).

4. Discussion

As the utilization of PB increases in the United States, there is accumulating evidence that treatment success is dependent on the accurate delivery of an adequate radiation dose to the prostate gland. The wide availability of robust treatment planning systems should allow most practitioners to obtain measures of implant quality in a timely fashion. This information should allow clinicians to modify their technique, if needed, resulting in improved dosimetric outcomes. We have used a rigorous dosimetric analysis to examine whether the incorporation of SES into our technique improves postimplant DQ. Our results indicate that the use of SES is associated with improved DQ as defined by CT scan 1 month following PB. Based on this analysis, we have moved to using SES for all subsequent implants.

A number of other investigators have utilized postimplant DQ to examine whether changes in technique or equipment result in improved dosimetric outcomes [3,18,23]. These modifications in technique or equipment run the gamut from the simple to the complex. Baird et al. observed that placing two marker seeds prior to PB (one at the base and another at the apex) resulted in better D90 values [3]. Stock et al. found that the use of a dual-phase ultrasound probe resulted in fewer patients with low D90 values compared to the use of a mechanical sector probe [18]. Zelefsky et al. at Memorial Hospital in New York have found that intraoperative computer-optimized conformal planning is associated with improved dosimetric outcomes [23]. It is the authors' opinion that SES is a treatment improvement device which, like the other examples listed above, can lead to better postimplant dosimetry.

This association between SES and improved implant dosimetry is quite plausible. In two large reports examining the spatial distribution of dose with the prostate gland, the region of the prostate most likely to receive a lower dose is the anterior base [14,17]. This region is close to the dorsal vein complex and sources placed near the anterior base could be more prone to embolize through the venous system. There is evidence that the use of SES results in lower rates of source embolization [21]. In this small sample the rate of seed embolization was lower with SES but the sample size is quite small and this difference was not statistically significant. We are presently examining the rate of source migration in a larger group of patients. Since the base is at the periphery of the implanted volume the migration of a few sources can result in significant unintended underdosage. One possible explanation of our results could be that SES allows for less source embolization, which is particularly important at the base, resulting in improved target coverage. It is important to point out that the use of loose seeds in the central portion of the prostate gland does not appear to result in seed embolization (no embolization seen in 20 patients treated with SES). Unlike the reports of

Table 2
Dosimetric quantifiers for the overall study population ($n = 40$) and stratified by implant technique

Variable	Overall ($n = 40$)	LS ($n = 20$)	SES ($n = 20$)	P-value
Mean (SD) V100 (%)	90.32 (5.1)	86.54 (3.7)	94.10 (2.9)	< 0.001
Mean (SD) V90 (%)	93.53 (4.2)	90.43 (3.2)	96.63 (2.2)	< 0.001
Mean (SD) V80 (%)	96.31 (3.0)	94.12 (2.6)	98.50 (1.3)	< 0.001
Mean (SD) D90 (Gy)	148.17 (21.9)	132.13 (11.6)	164.2 (17.3)	< 0.001
D90 >140 Gy (%)	27 (67)	7 (35)	20 (100)	< 0.001

others, we did not systematically identify the regions that were underdosed. We are in the process of performing sector analysis in a larger group of patients. At present it is our opinion that in the majority of cases the base region is more likely to be underdosed.

At least three criticisms of this analysis deserve mention. First, this is a non-randomized retrospective comparison. All patients in this report were treated by the same PB team including a single radiation oncologist and a single urologist. Other than changing the type of source used for the procedure all other variables have remained the same. We chose to compare the SES group with the most recent 20 LS cases rather than the entire LS experience because we have documented a steep learning curve for this procedure and we were seeking to minimize any temporal trends [11]. There are small differences in the prostate size and the activity per unit volume implanted between the SES and LS groups. It is possible that a 10% increase in activity will improve the V100 and D90 by 2–3% but the magnitude of improvement we observed was larger than this. These variables were included in the multivariate analysis and the source type continued to be the only independent predictor of implant quality. As much as the investigators have attempted to keep all variables constant, the potential for residual confounding exists.

Secondly, one may question the use of an intermediate endpoint such as V100 or D90. As has been previously mentioned, limited information does suggest that measures of implant adequacy can be correlated with disease-free survival. The authors hasten to point out, however, that no measure of implant adequacy has been associated with overall survival or prostate cancer specific survival. The correlation between some measure of radiation dose to the prostate gland and survival (if one exists) can only be examined in large cohorts of patients with long follow-up. In the meantime, there is evidence that the DQ used in this report are reliable [5,18]. The authors believe that DQ can provide clinicians with important information that can be utilized as part of a continuous quality improvement process to maximize the likelihood of an adequate prostate implant.

Finally the DQ used in this report rely on prostate delineation on the postimplant CT scans. There are two reports that indicate that there is a large amount of disagreement between reviewers when different reviewers are asked to outline the prostate on identical images [1,12]. In this report, the prostate was outlined by a single reviewer (WRL) so interobserver reliability was not a factor in prostate delineation. The single reviewer was not aware of the technique used (LS versus SES) in each case.

5. Conclusions

This non-randomized retrospective comparison of transperineal preplanned prostate brachytherapy indicates that the use of SES results in improved postimplant dosimetry compared to the use of LS.

References

[1] Al-Qaisieh B, Ash D, Bottomley DM, Carey BM. Impact of prostate volume evaluation by different observers on CT-based post-implant dosimetry. Radiother Oncol 2002;62:267–273.

[2] Bahnson RR, Hanks GE, Huben RP, et al. NCCN Practice Guidelines for Prostate Cancer. Oncology (Huntingt) 2000;14:111–119.

[3] Baird MC, Holt RW, Selby TL. Improvement of transperineal implant dosimetry by intraoperative cystoscopic confirmation of prostate anatomy. J Urol 2000;164:406–410.

[4] Battermann JJ. I-125 implantation for localized prostate cancer: the Utrecht University experience. Radiother Oncol 2000;57:269–272.

[5] Bice Jr WS, Prestidge BR, Grimm PD, et al. Centralized multiinstitutional postimplant analysis for interstitial prostate brachytherapy. Int J Radiat Oncol Biol Phys 1998;41:921–927.

[6] Blasko JC, Grimm PD, Ragde H. Brachytherapy and organ preservation in the management of carcinoma of the prostate. Semin Radiat Oncol 1993;3:240–249.

[7] Blasko JC, Grimm PD, Sylvester JE, Badiozamani KR, Hoak D, Cavanagh W. Palladium-103 brachytherapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 2000;46:839–850.

[8] Critz FA, Levinson AK, Williams WH, Holladay CT, Griffin VD, Holladay DA. Simultaneous radiotherapy for prostate cancer: 125I prostate implant followed by external-beam radiation [see comments]. Cancer J Sci Am 1998;4:359–363.

[9] Fuks Z, Leibel SA, Wallner KE, et al. The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation. Int J Radiat Oncol Biol Phys 1991;21:537–547.

[10] Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin 2001;51:15–36.

[11] Lee WR, deGuzman AF, Bare RL, Marshall MG, McCullough DL. Postimplant analysis of transperineal interstitial permanent prostate brachytherapy: evidence for a learning curve in the first year at a single institution. Int J Radiat Oncol Biol Phys 2000;46:83–88.

[12] Lee WR, Roach M, Michalski J, Moran B, Beyer D. Inter-observer variability leads to significant differences in quantifiers of prostate implant adequacy. Int J Radiat Oncol Biol Phys 2002;54(2):457–461.

[13] Nag S, Bice W, DeWyngaert K, Prestidge B, Stock R, Yu Y. The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis. Int J Radiat Oncol Biol Phys 2000;46:221–230.

[14] Prestidge BR, Bice WS, Walker ES, Sarosdy MF. Spatial dose-mapping following transperineal interstitial permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2000;48:148.

[15] Ragde H, Korb LJ, Elgamal AA, Grado GL, Nadir BS. Modern prostate brachytherapy. Cancer 2000;89:135–141.

[16] Roberson PL, Narayana V, McShan DL, Winfield RJ, McLaughlin PW. Source placement error for permanent implant of the prostate. Med Phys 1997;24:251–257.

[17] Sidhu S, Morris WJ, Spadinger I, et al. Prostate brachytherapy postimplant dosimetry: a comparison of prostate quadrants. Int J Radiat Oncol Biol Phys 2002;52:544–552.

[18] Stock RG, Stone NN, Kao J, Iannuzzi C, Unger P. The effect of disease and treatment-related factors on biopsy results after prostate brachytherapy: implications for treatment optimization. Cancer 2000;89:1829–1834.

[19] Stock RG, Stone NN, Lo YC, Malhado N, Kao J, DeWyngaert JK. Postimplant dosimetry for (125)I prostate implants: definitions and factors affecting outcome. Int J Radiat Oncol Biol Phys 2000;48:899–906.

[20] Stock RG, Stone NN, Tabert A, Iannuzzi C, DeWyngaert JK. A dose-response study for I-125 prostate implants. Int J Radiat Oncol Biol Phys 1998;41:101–108.
[21] Tapen EM, Blasko JC, Grimm PD, et al. Reduction of radioactive seed embolization to the lung following prostate brachytherapy. Int J Radiat Oncol Biol Phys 1998;42:1063–1067.
[22] Zelefsky MJ, Whitmore Jr WF. Long-term results of retropubic permanent 125iodine implantation of the prostate for clinically localized prostatic cancer. J Urol 1997;158:23–29 discussion 29–30.
[23] Zelefsky MJ, Yamada Y, Cohen G, et al. Postimplantation dosimetric analysis of permanent transperineal prostate implantation: improved dose distributions with an intraoperative computer-optimized conformal planning technique. Int J Radiat Oncol Biol Phys 2000;48:601–608.

ATTACHMENT 3

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, pp. 397–399, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2003.10.034

CLINICAL INVESTIGATION **Prostate**

THE USE OF LINKED SEEDS ELIMINATES LUNG EMBOLIZATION FOLLOWING PERMANENT SEED IMPLANTATION FOR PROSTATE CANCER

BASHAR AL-QAISIEH, M.SC.,* BRENDAN CAREY, F.R.C.R.,† DAN ASH, F.R.C.R.,† AND DAVID BOTTOMLEY, F.R.C.R.†

*Department of Medical Physics and †Regional Cancer Treatment Center, Cookridge Hospital, Leeds, United Kingdom

Purpose: A number of reports of ^{125}I seed migration to the lungs after prostate brachytherapy have been published. There are, however, very limited data available on how to reduce the risk of this event. The purpose of the present report is to determine whether seed embolization to the lungs can be minimized by using stranded seeds alone for brachytherapy.

Methods and Materials: Between December 2001 and December 2002, 238 patients with early prostate cancer were treated with prostate brachytherapy as monotherapy using ^{125}I stranded seeds (RAPIDStrand) exclusively. All patients had fluoroscopy during the implant and immediate postimplant radiographs of the pelvis. A sample of 100 patients had chest radiographs performed, on average, 55 days after implant. To determine the ease, or lack of ease, with which these ^{125}I seeds could be visualized, 4 patients who did not have prostate cancer and who were having routine chest radiographs as part of their management for other cancers consented to have posteroanterior and lateral radiographs performed with inactive ^{125}I seeds taped to the skin of the thorax. All radiographs were reviewed by a single radiologist.

Results: The number of seeds noted on the postimplant radiographs corresponded to the number of implanted seeds in all 238 cases: There was, therefore, no evidence of seed embolization immediately postimplant. On review of the 100 chest radiographs, no embolized seeds were found.

Conclusion: No evidence of seed embolization was observed with the use of stranded ^{125}I seeds as used for prostate brachytherapy. © 2004 Elsevier Inc.

Prostate, Brachytherapy, Iodine-125, Migration, Pulmonary embolism.

INTRODUCTION

Prostate brachytherapy is an increasingly popular method of treatment for early-stage prostate cancer. Current seed implantation technique is generally based on peripheral loading (1–3) to reduce the dose to the urethra. This technique often requires seeds to be implanted adjacent to the prostatic margin, which may be associated with seed embolization to the lungs (3–16).

Steinfeld *et al.* (11) were the first to report pulmonary seed embolization after prostate brachytherapy. The likely explanation is that an ^{125}I seed (4.5 mm in length and 0.8 mm in diameter) is small enough to migrate through the dense venous plexus surrounding the prostate. Seeds entering the venous system access the right heart and then embolize and become lodged in the lungs (3). Seed migration to other sites has been reported (17, 18) and is most likely explained by the presence of a right-to-left intracardiac shunt.

There have been a number of literature reports addressing the risk of seed embolization (19–21). The aim of this study was to investigate the incidence of ^{125}I seed embolization with stranded seeds only (RAPIDStrand).

METHODS AND MATERIALS

Transperineal prostate brachytherapy at Cookridge Hospital began in 1995 and, to date, over 1100 implants have been performed. Implant techniques have evolved over the years, but in essence are still based on the preplan method. Between 1995 and September 1999, all patients were implanted with ^{125}I free seeds. After this, RAPIDStrand was introduced. Initially, these stranded seeds were restricted to needles placed at the periphery of the prostate with no extracapsular placement. The periurethral areas were implanted with free seeds. Since December 2001, RAPIDStrand has been used exclusively for all our prostate implants.

Between December 2001 and December 2002, 238 pa-

Reprint requests to: Bashar Al-Qaisieh, Medical Physics Department, Cookridge Hospital, Hospital Lane, Leeds LS16 6QB, United Kingdom. Tel: (+44-0) 113-3924399; Fax: (+44-0) 113-3924122; E-mail: bashar@medphysics.leeds.ac.uk

Received Jun 2, 2003, and in revised form Oct 7, 2003. Accepted for publication Oct 15, 2003.

tients were implanted. The average treated prostate volume was 31.9 cc (range, 11.7–54.0 cc). The average number of seeds implanted was 81 (range, 44–115 seeds) with average activity of 0.460 U (range, 0.413–0.492 U) loaded into an average of 30 needles (range, 20–40 needles) to deliver a prescribed dose of 145 Gy (1, 2).

All patients had fluoroscopy during the implant as per normal procedure for this institution. One hundred consecutive patients had chest radiographs (posteroanterior [PA]), performed on average 55 days after implant (median, 53 days; range, 24–115 days). These radiographs were reviewed by a single radiologist (B.C.), who is familiar with prostate brachytherapy.

Four patients who did not have prostate cancer consented to have chest radiographs to act as a reference group. None of these 4 patients had any known chest pathology but did require chest radiography as part of their management. The purpose of this was to explore the ease of visualization of ^{125}I seeds on PA and lateral chest radiographs. Inactive ^{125}I seeds were taped to various parts of the chest wall, and the ease of identification was noted over different tissues (lung parenchyma, heart, spine, and ribs).

RESULTS

(*A*) The seed count on immediate postimplant pelvic radiographs equated to the number of implanted seeds in all 238 patients. There was, therefore, no evidence of seed loss immediately after the implant. (*B*) No evidence of seed embolization to the lungs was observed on the sample of 100 consecutive chest radiographs. (*C*) Seeds were clearly visible on all 4 control patients—both PA and lateral projections.

DISCUSSION

In common with other groups, we did occasionally observe seed embolization to the lungs with the use of free ^{125}I seeds. The clinical consequences relating to these embolized seeds were considered negligible—the main concern was the reduction in the number of seeds contributing to dose in the prostate gland itself. The introduction of stranded seeds (22) was considered an advantage by our group and was therefore incorporated into our brachytherapy technique. Stranded seeds have been reported to improve the implant dosimetry (23), as well as reduce the possibility of seed embolization from 11.6% to 0.7% compared to free seeds (3). The results of our study suggest that the exclusive use of RAPIDStrand seeds may eliminate the risk of seed embolization to the lungs.

RAPIDStrand was initially used in our center in conjunction with a few free seeds that were implanted around the urethra. This technique was adopted to avoid excess preurethral dosage. Free seeds were loaded in brachytherapy needles using spacers that left sufficient gaps between free seeds, as planned. Recently, this technique has been replaced by one using only linked seeds for the whole implant. To maintain an acceptable urethral dose, a split needle method was introduced. For example, if a plan produces a single needle containing 2 seeds at 0.0-mm retraction from the base and another 2 seeds at 40.0-mm retraction, this needle is divided into 2 needles (splits). The first needle contains 2 linked seeds to be implanted at 0.0-mm retraction, and the second needle contains another 2 linked seeds to be implanted at 40.0-mm retraction using the same coordinate on the ultrasound template. This method may increase seed fixity and, hence, improve dosimetry and eliminate seed migration, as well as avoid an excessive urethral dose.

RAPIDStrand is ^{125}I seeds linked by a braided, tissue-absorbable suture material made of Polyglactin 910. Experimental i.m. implantation studies of Polyglactin 910 show absorption begins as a loss of tensile strength followed by a loss of mass. The suture material retains approximately 75% of the original tensile strength at 2 weeks postimplantation. All of the original tensile strength is lost between 4 and 5 weeks postimplantation. Absorption is essentially complete between 56 and 70 days (RAPIDStrand instructions for use). The seeds, however, should be well epithelialized within the gland by this time, and so migration and embolization are unlikely to occur even after suture absorption. Our study supports this view with no evidence of any seed embolization observed.

Visualization of ^{125}I seeds on chest radiographs might be influenced by a number of factors. If the seed is lying behind high-attenuation regions, such as bony structures or the heart, it might be less visible on the chest radiographs. ^{125}I seeds are, however, very radiopaque (silver and titanium shell), and there was no problem identifying these seeds on the chest radiographs of the control patient group, regardless of site or radiographic projection. Furthermore, all chest radiographs were reviewed by an experienced radiologist familiar with prostate brachytherapy, who had the specific purpose of identifying seeds. We do not consider, therefore, that seeds could have been overlooked or rendered inconspicuous in our study.

CONCLUSION

The exclusive use of stranded seeds for prostate brachytherapy is associated with a negligible risk of seed embolization to the lungs. This should minimize any detrimental effect on prostate dosimetry resulting from possible seed loss, as well as eliminate any potential risk of radiation toxicity to organs affected by seed embolization.

REFERENCES

1. Nath R, Anderson LL, Luxton G, *et al.* Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Committee Task Group No. 43. *Med Phys* 1995;22: 209–234.

2. Luse RW, Blasko J, Grimm P. A method of implementing the American Association of Physicists in Medicine Task Group-43 dosimetry recommendations for 125I transperineal prostate seeds implants on commercial treatment planning systems. *Int J Radiat Oncol Biol Phys* 1997;37:737–741.
3. Tapen EM, Blasko JC, Grimm PD, *et al.* Reduction of radioactive seed embolization to the lung following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998;42:1063–1067.
4. Ankem MU, DeCarvalho VS, Harangozo AM, *et al.* Implications of radioactive seed migration to the lungs after prostate brachytherapy. *Urology* 2002;59:555–559.
5. Guigauri P, Watkins MW. Lung embolization of prostate cancer brachiotherapy seeds: Incidental finding during left heart catheterization (Letter). *J Invasive Cardiol* 2002;148: A22.
6. Gupta S, Nag S, Gupta J. Pulmonary embolization of permanently implanted radioactive iodine-125 seeds. *Endocuriether Hypertherm Oncol* 1993;9:27–31.
7. Merrick GS, Butler WM, Dorsey AT, *et al.* Seed fixity in the prostate/periprostatic region following brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;46:215–220.
8. Hempel M, Bruggmoser G, Wannenmacher M. A rare complication in interstitial therapy with iodine-125 seeds: "Embolization of seed into the lung." *Strahlenther Onkol* 1988;164: 531–532.
9. Hunttner S, Lengsfeld M, Scholz H. A rare route for the loss of a I-125 seed after the interstitial therapy of prosthetic carcinoma. *Urologe-Ausgabe* 1992;31:96–97.
10. Sommerkamp H, Rupprecht M, Wannenmacher M. Seed loss in interstitial radiotherapy of prostatic carcinoma with I-125. *Int J Radiat Oncol Biol Phys* 1988;14:389–392.
11. Steinfeld AD, Donahue BR, Planine L. Pulmonary embolization of Iodine-125 seeds following prostate implantation. *Urology* 1991;37:149.
12. Van't Riet A, Te Loo HJ, Ypma AF, *et al.* Ultrasonically guided transperineal seed implantation of the prostate: Modification of technique and qualitative assessment of implants. *Int J Radiat Oncol Biol Phys* 1992;24:555–558.
13. Welle GJ, Quinn K. Pulmonary embolization of iodine-125 implants. *Am J Roentgenol* 1992;159:218.
14. Dafoe-Lambie JC, Abel LJ, Blatt HJ, *et al.* Radioactive seed embolization to the lung following prostate brachytherapy. *W V Med J* 2000;96:357–360.
15. Eshleman JS, Davis BJ, Wilson TM, *et al.* Radioactive seed migration to the chest following transperineal interstitial prostate brachytherapy for early stage prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2001;51:297–298.
16. Grimm PD, Blasko JD, Ragde H, *et al.* Migration of iodine-125 and palladium-103 seeds to the lung after transperineal brachytherapy for prostate cancer. *Endocuriether Hypertherm Oncol* 1993;9:50.
17. Davis BJ, Bresnahan JF, Stafford SL, *et al.* Prostate brachytherapy seed migration to a coronary artery found during angiography. *J Urol* 2002;1683:1103.
18. Davis BJ, Pfeifer EA, Wilson TM, *et al.* Prostate brachytherapy seed migration to the right ventricle found at autopsy following acute cardiac dysrhythmia. *J Urol* 2000;1645:1661.
19. Nag S, Scaperoth DD, Badalament R, *et al.* Transperineal palladium 103 prostate brachytherapy: Analysis of morbidity and migration. *Urology* 1995;45:87–92.
20. Nag S, Vivekanandam S, Martfinez-Monge R. Pulmonary embolization of permanently implanted radioactive palladium-103 seeds for carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1997;39:667–670.
21. Older RA, Synder B, Krupski TL, *et al.* Radioactive implant migration in patients treated for localized prostate cancer with interstitial brachytherapy. *J Urol* 2001;165:1590–1592.
22. Kumar PP, Good RR. Vicryl carrier for I-125 seeds: Percutaneous transperineal insertion. *Radiology* 1986;159:276.
23. Lee WR, deGuzman AF, Tomlinson ST, *et al.* Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy. *Radiother Oncol* 2002;65:123–127.

ATTACHMENT 4

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, pp. 419–425, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2003.10.050

CLINICAL INVESTIGATION **Prostate**

RADIOACTIVE SEED MIGRATION TO THE CHEST AFTER TRANSPERINEAL INTERSTITIAL PROSTATE BRACHYTHERAPY: EXTRAPROSTATIC SEED PLACEMENT CORRELATES WITH MIGRATION

JEFFREY S. ESHLEMAN, M.D.,* BRIAN J. DAVIS, M.D., PH.D.,* THOMAS M. PISANSKY, M.D.,* TORRENCE M. WILSON, M.D.,† MICHAEL G. HADDOCK, M.D.,* BERNARD F. KING, M.D.,‡ CHARLES H. DARBY, M.S.,§ WAYNE N. LAJOIE, B.S.,* AND ANN L. OBERG, PH.D.§

*Division of Radiation Oncology, Departments of †Urology and ‡Diagnostic Radiology, and §Division of Biostatistics, Mayo Clinic, Rochester, MN

Purpose: To examine the incidence of seed migration detected on chest X-ray and to identify the predictors associated with its occurrence.

Methods and Materials: Between May 1998 and April 2000, 102 patients underwent permanent prostate brachytherapy at our institution and 100 were eligible for the study. Chest X-rays obtained at follow-up were examined for the number and location of seeds. The patient and treatment variables potentially associated with the occurrence and number of seed migrations were analyzed.

Results: One or more seeds were identified on the chest X-rays of 55 (55%) of 100 patients. The mean number of intrathoracic seeds in patients with migration was 2.2 (range, 1–10), and the proportion of seeds that migrated to the thorax was 0.98%. The rate of extraprostatic seeds planned was 43.9%, and postimplant CT identified 37.9% in such a location. The number of seeds planned for extraprostatic placement and below the apex were statistically significant ($\alpha = 0.05$) predictors in univariate logistic analysis. Multivariate analysis revealed the planned number of extraprostatic seeds as the only statistically significant predictor ($p = 0.04$).

Conclusion: Extraprostatic placement of loose seeds is associated with an increased likelihood for, and frequency of, seed migration to the thorax. Nonetheless, the small proportion of implanted seeds that migrated (≤1%) is highly unlikely to have significant dosimetric consequences. © 2004 Elsevier Inc.

Brachytherapy, ^{125}I, Migration, Prostatic neoplasms, Radiotherapy.

INTRODUCTION

In 2003, an estimated 220,900 men in the United States were diagnosed with adenocarcinoma of the prostate and 28,900 men died of this cancer (1). With the advent of prostate-specific antigen screening, most prostate cancer diagnoses are made in the early stages. An increasingly used option in the management of early-stage prostate cancer is transperineal interstitial permanent prostate brachytherapy (TIPPB) (2).

A unique property of TIPPB is the possibility of radioactive seed migration. In 1988, Hempel *et al.* (3) reported on a patient who underwent ^{125}I interstitial therapy for carcinoma of the anus and was later found to have metallic seeds on chest X-ray (3). Subsequently, Steinfeld *et al.* (4) reported chest migration of a radioactive seed after TIPPB. Gupta *et al.* (5) later reported seed migration to the chest from various anatomic sites after interstitial brachytherapy. In recent years, the increased use of TIPPB has led to multiple reports of radioactive seed migration to the chest (4, 6–13). Published rates, as summarized in Table 1, range from 0.6% to 29% of patients with one or more seeds found on a postimplant chest X-ray (CXR). Published patient and treatment parameters influencing the incidence and rate of seed migration include the use of Vicryl sutures, number of seeds implanted, planning volume, and number of loose seeds placed (7, 10).

The basis of radioactive seed migration seems clear; the prostatic capsule has a rich venous plexus with vessels large enough to accommodate seeds. Seeds placed extraprostatically have access to this plexus and often migrate away from their intended position via access to the venous circulation. Through the venous pathway, seeds migrate through the inferior vena cava, right chambers of the heart and into the pulmonary circulation. Because of their size and rigid-

Reprint requests to: Brian J. Davis, M.D., Ph.D., Division of Radiation Oncology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. Tel: (507) 284-3191; Fax: (507) 284-0079; E-mail: davis.brian@mayo.edu

Originally presented at the 43rd Annual Meeting of the American Society for Therapeutic Radiology and Oncology, November 2001.

Received Jun 26, 2003. Accepted for publication Oct 15, 2003.

Table 1. Chest migration in reported TIPPB series

Study	Isotope	Patients with seed migration to chest (%)	Rate of seed migration to chest (%)	Maximum seeds to migrate in 1 patient (*n*)
Present study	^{125}I and ^{103}Pd	55.0% (55/100)	0.98% (119/12,135)	10
Grimm *et al.* (12)	^{125}I and ^{103}Pd	17.6% (39/221)	Not reported	3
Merrick *et al.* (7)	^{125}I (Rapid STRAND in periphery)	21.4% (18/84)	0.18% (24/13,467)	Not reported
	^{103}Pd	22.2% (16/72)	0.28% (29/10,338)	Not reported
	Overall	21.8% (34/156)	0.22% (53/23,805)	Not reported
Nag (8)	^{103}Pd	17.8% (19/107)	0.30% (32/10,612)	2
Older (13)	^{103}Pd	29.0% (32/110)	Not reported	4
Steinfeld *et al.* (4)	^{125}I	20.0% (1/5)	0.80% (5/600)	5
Tapen *et al.* (10)	^{125}I (Rapid STRAND in periphery)	0.7% (1/143)	Not reported	2
	^{125}I loose	10.0% (1/10)	Not reported	Not reported
	^{103}Pd	11.0% (15/126)	Not reported	Not reported
	Overall	5.9% (17/289)	Not reported	Not reported

Abbreviation: TIPPB = transperineal interstitial permanent prostate brachytherapy.

ity, seeds lodge in the end arterioles of the pulmonary system where, owing to their metallic content, they can be easily visualized by CXR.

To date, no untoward clinical consequences have been reported when pulmonary embolization has occurred (4, 6–13). However, it is conceivable that seeds could migrate or become entrapped in other organ systems. In this regard, autopsy-documented evidence has recently been published of seeds lodged in the right ventricle of the heart (14) and in a coronary artery as visualized by angiography (15).

Other potential consequences of seed migration include dosimetric consequences (16). Seeds lost to migration detract from the overall dose meant to cover the planning target volume. Merrick *et al.* (7) reported that pulmonary seed embolization accounted for only 10% of the seeds absent after orthogonal films were taken of the pelvis after implantation. Thus, CXR detection alone may significantly under represent the total seed loss from the target volume.

Migration rates have been linked to technical differences in TIPPB, which have been previously reviewed (17). Many institutions perform a modified peripheral loading technique in which loose seeds are placed. Most seeds are placed in the periphery of the gland to administer a homogenous dose and limit severe overdosing to the urethra. A typical margin of 3–5 mm is planned around the prostate (18) to account for extraprostatic tumor extension (19, 20), the accuracy of delivering the radiation dose to the target volume (21, 22), and the accuracy of the imaging technology used in the procedure. Other factors influencing migration rates may include both patient and tumor characteristics. The purpose of this study was to examine both clinical and treatment-related factors associated with migration of seeds to the thorax.

METHODS AND MATERIALS

Patient characteristics

The patient characteristics are given in Table 2. Between May 1998 and April 2000, 102 patients with Stage T1-T2 prostate cancer underwent TIPPB at our institution of whom 100 were included in this study. All patients underwent transrectal ultrasound (TRUS)-based planning using a modified peripheral loading technique and loose seed placement. Post-TIPPB dosimetry was evaluated by CT within 30 days after the date of the procedure. PA and lateral CXRs obtained at follow-up were examined for the number and location of seeds. Patient and treatment variables potentially associated with the occurrence and number of seed migrations were analyzed.

Preimplant planning

All patients underwent TRUS-based preplanning using the Theraplan Plus 3.0 system (Theratronics, MDS Inc., Toronto, Ontario, Canada). The planning target volume was created by placing a 3–5-mm margin around the prostate, except in the posterior and superior directions. Posteriorly, in proximity to the rectum, and superior to the bladder base, a smaller margin was used.

TIPPB procedure and postimplant CT scanning

The TIPPB procedure has been previously described (23); it includes the use of a Mick applicator and a modified peripheral loading technique. Ninety-seven patients underwent ^{125}I implantation and three underwent ^{103}Pd implantation. Ninety-nine patients were treated with TIPPB as monotherapy, and one received combination external beam radiotherapy and TIPPB. All patients were admitted postoperatively to the hospital overnight, and a Foley catheter was placed in each. Urine and Foley catheter bags were inspected and surveyed for displaced seeds. Patients rou-

Table 2. Patient and treatment characteristics

Characteristic	Patients (*n*)	Mean (range)
Age (y)		68.8 55–70
Tumor stage (1997 AJCC)		
T1c	63 (63)	
T2a	35 (35)	
T2b	2 (2)	
Pretreatment PSA (ng/mL)		6.3 0.7–16.3
PSA (ng/mL)		
0.0–4.0	24 (24)	
4.1–10.0	64 (64)	
>10.0	12 (12)	
Gleason score		6 (4–7)
4–5	15 (15)	
6–7	85 (85)	
Pretreatment ultrasound volume (cm^3)		43.3 (16–98)
Postimplant CT volume (cm^3)		56.7 (20–124)
Time to postimplant CT (days)		5.7 (0–57)
Radioisotope (Gy)		
^{125}I	97 (97)	
^{103}Pd	3 (3)	
Seeds planned (*n*)		113.1 (58–192)
Seeds placed (*n*)		123.8 (60–214)
Needles implanted (n)		30.3 (18–50)
mCi per source (^{125}I only)		0.4 (0.3–0.5)
Total mCi implanted (^{125}I only)		48.1 (22.2–82.2)

Abbreviations: AJCC = American Joint Committee on Cancer; PSA = prostate-specific antigen.

Data in parentheses are percentages, unless otherwise noted.

tinely underwent postimplant CT scanning within 2 days after their procedure. The prostate was contoured on the CT image by the treating radiation oncologist. Postimplant dosimetric analysis was performed according the American Brachytherapy Society recommendations (24).

Statistical analysis

The preplans were reviewed and the following information was recorded: preimplant prostate size in cubic centimeters as determined by TRUS planimetry and prolate spheroid calculation, number of needles planned, total number of seeds planned and placed, and postimplant prostate size in cubic centimeters by CT contouring. Preplanning ultrasonography and postimplant CT were then carefully reviewed for peripheral and extraprostatic seed placement. Extraprostatic seed placement was defined as any digitally reconstructed seed falling completely outside the CT-contoured prostatic capsule or planimetric margin. Peripheral seed placement was defined as any extraprostatic seed or any digitally reconstructed seed falling on the CT-contoured prostatic capsule or margin. Seeds planned and placed above the base and below the apex were analyzed separately as well as included in the extraprostatic group. An example of a preplan TRUS image identifying extraprostatic and peripherally labeled digitally reconstructed seeds is shown in Fig. 1.

All patients whose records were used in this analysis had previously provided consent for use of their records in retrospective medical research. Univariate analyses were prepared and examined to ascertain any transformations that would be necessary before subsequent model building ensued. Predictors were transformed using the natural logarithm function to reduce skewness of distribution if appropriate. Univariate and multivariate logistic models of occurrence of seed migrations were performed.

RESULTS

Of the 102 patients whose medical records were considered for use in this study, 1 did not have a postoperative CXR and 1 refused research authorization. Thus, 100 patients with one or more postimplant CXR were evaluated. One or more seeds were identified on the CXRs of 55 (55%) of 100 patients. A total of 119 (0.98%) of 12,135 seeds implanted were identified on CXR. The mean number of intrathoracic seeds in patients with migration was 2.2 (median, 2; range, 1–10). The distribution of seeds on CXR (Table 3) was 11 right upper lobe, 3 right middle lobe, 74 right lower lobe, 3 left upper lobe, and 26 left lower lobe and 2 autopsy proven seeds in the right cardiac ventricle. The proportion of extraprostatic seeds planned was 43.9%, and 37.9% were actually placed in an extraprostatic location as ascertained by postoperative CT imaging (Table 4). The number of seeds planned for extraprostatic placement and inferior to the apex was a statistically significant predictor of seed migration in univariate logistic analyses at the $\alpha = 0.05$ level (Table 5).

Three additional predictors were suggestive of significance at or below $\alpha = 0.14$. These included the number of seeds planned for implantation above the prostate base, number of peripheral seeds for implantation, and natural log of time from the procedure to the first CXR. All five predictors were tested in multiple logistic models via a stepwise model building process. *A priori,*, a four-predictor model was also considered on the basis of our knowledge. The predictors considered were the number of seeds planned for implantation at the prostate periphery and below the apex, the total number of seeds planned for placement, and the interval (expressed as natural logarithm [LnT]) from TIPPB until the first CXR. Subsequent evaluation indicated that the multiple predictor models were unstable and provided no usable information. Consequently, multivariate analysis revealed the planned number of extraprostatic seeds as the only statistically significant predictor ($p = 0.04$). LnT was suggestive of an effect ($p = 0.053$).

No toxicity was reported from chest migration of the radioactive seeds. Although the patient with two ^{125}I seeds found within the right ventricle died of a cardiac event, he had had a long history of heart disease, and the cause of death was not attributed to the embedded seeds (14).

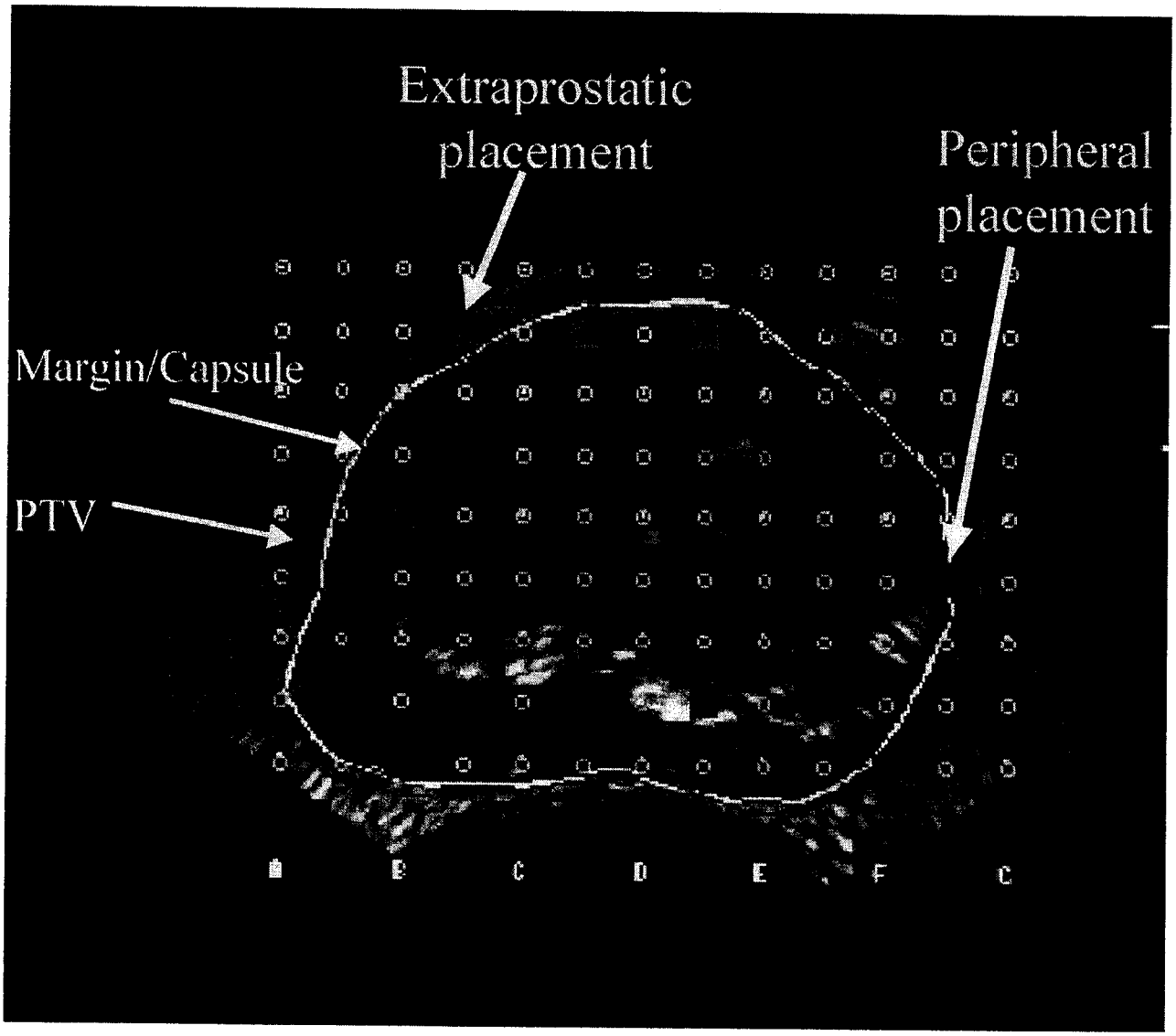


Fig. 1. Preimplant planning ultrasound scan. Extraprostatic seed placement defined as any digitally reconstructed seed falling completely outside contoured prostatic capsule or margin on ultrasound imaging. Peripheral seed placement defined as any extraprostatic seed plus any digitally reconstructed seed falling on contoured prostatic capsule or margin on ultrasound imaging. Similar method also applied to evaluation of postimplant CT scans.

Table 3. Seed migration to chest

Lobe of lung	Patients (*n*)	Total seeds migrating to chest (%)	Range
RUL	7	11/119 (9)	1.0–3.0
RML	2	3/119 (3)	1.0–2.0
RLL	41	74/119 (63)	1.0–8.0
LUL	3	3/119 (3)	1.0–2.0
LLL	19	26/119 (22)	1.0–2.0
Heart*	1	2/119 (2)	—

Abbreviations: RUL = right upper lobe; RML = right medial lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe.

* Autopsy proven.

DISCUSSION

We report the postimplant seed migration rate to the chest in 100 of the first 102 consecutive patients undergoing TIPPB at our institution. Fifty-five percent of the 100 patients had seed migration to the chest after TIPPB. As summarized in Table 1, this rate was greater than in any previous study on seed migration. However, the total number of seeds found on CXR accounted for <1% of seeds implanted into the prostate and periprostatic tissue. This latter finding is consistent with that of other studies pertaining to the use of loose seeds. The results of the present study differ from many others in that the percentage of seeds planned for extraprostatic placement exhibited a high correlation with seed migration. It also differs in that a thorough review of both PA and lateral CXRs before and after TIPPB was performed.

Table 4. Peripheral and extraprostatic seed placement by pre- and postimplant imaging

Seed placement	Planned preimplant TRUS	Actual postimplant CT
Average proportion of extraprostatically placed seeds	39% (43.9/113.1)	31% (37.9/123.8)
Average proportion of peripherally placed seeds	60% (68.3/113.1)	47% (58.6/123.8)
Average proportion of seeds placed inferior to the apex	7% (8/113.1)	4% (4.7/123.8)
Average proportion of seeds placed superior to the base	6% (7/113.1)	3% (3.6/123.8)

Abbreviation: TRUS = transrectal ultrasonography.

The high rate of seed migration found in this report may be attributed to several factors. First, CXRs were available for review in >98% of the 100 study patients. This patient evaluation rate contrasts with several other studies such as that of Older (13) in which only 110 (60%) of 183 patients had postimplant CXRs available for review. Whether the 60% of patients was representative of the group as a whole was not indicated, so the overall seed migration rate in their patients may have been different. In the present study, preoperative CXRs were available for comparison allowing selective identification of migrated seeds even in the presence of multiple surgical clips in the chest from prior coronary artery bypass grafts or other surgical interventions. The identification of seeds from CXRs showing multiple surgical clips in patients with prior chest surgery without pre-TIPPB CXRs for comparison may add a source of uncertainty. From a review of plain film imaging, it is clear that diagnostic-quality PA and lateral CXRs more thoroughly and readily identify seeds than would a limited PA view on a fluoroscopic simulator. Some patients had seeds near the diaphragm, which were only identifiable as such on a lateral CXR. Finally, the results of our study suggest that the timing of the CXR may be relevant to the occurrence of seed migration. The greater the duration between TIPPB and subsequent CXR, the more likely that seed migration might be detected. In our series, CXRs were usually obtained 2–3 months after TIPPB; CXRs were obtained much sooner after the procedure in some other reports. This observation is consistent with that of Merrick *et al.* (7) who observed an increasing rate of seed migration depending on the timing of post-TIPPB CXR.

Table 5. Univariate analysis of patient and treatment parameters with seed migration to chest

Parameter	*p*
Total seeds planned for extraprostatic placement (TRUS)	0.03
Total seeds planned for placement inferior to the apex (TRUS)	0.03
Total seeds planned for peripheral placement (TRUS)	0.06
Time from implant to CXR	0.14
Total seeds planned for placement superior to base (TRUS)	0.21
Total number of seeds planned	0.35
Total number of seeds placed	0.36
Radiation oncologist	0.38
Seeds placed peripherally (postimplant CT)	0.45
Seeds placed extraprostatically (postimplant CT)	0.55
Seeds placed inferior to apex (postimplant CT)	0.60
Postimplant CT volume	0.63
Pretreatment TRUS volume	0.86
Actual seeds placed superior to base (by postimplant CT)	0.92

Abbreviations: TRUS = transrectal ultrasonography; CXR = chest X-ray.

TRUS used for preplanning; CT used for postimplant imaging and dosimetry analysis.

In the present study, regression analysis revealed that extraprostatic seed placement in the TRUS preplan correlated with migration. This finding is consistent with observations made during TIPPB in which seed migration was witnessed by fluoroscopy, particularly as seeds were placed anterior to the prostate where abundant venous drainage exists (25). The anterior and lateral periprostatic locations appear more prone to seed migration than other periprostatic locations. Nonetheless, seed migration has also been observed with intraprostatic seed placement, albeit much less frequently than with extraprostatic placement. No other study, to our knowledge, has confirmed the clinical observation that extraprostatic seed placement as per TRUS preplanning correlates with migration. Treatment of extraprostatic extension of prostate cancer is accomplished using a 3–5-mm dosimetric margin (19, 20, 26). TIPPB may treat extraprostatic extension with placement of a portion of the seeds in extraprostatic locations (27). In a survey report on experienced brachytherapists by Prete *et al.* (28), 53% of respondents reported using a 5-mm treatment margin. On the basis of this response and radiation dosimetric considerations, it is likely that the placement of some seeds in extraprostatic locations remains a common and arguably rational approach to TIPPB (27). In a related study by Butzbach *et al.* (29), examination of treatment margins and seed placement was conducted. Seeds were implanted in extraprostatic locations only at the prostatic base and apex, and the treatment margins were judged adequate to treat extraprostatic extension by postimplant CT-based dosimetric analysis. Nonetheless, and in principle, it appears possible that a dosimetric margin may be achieved if intraprostatic peripheral seed location is within 1–2 mm of the prostatic capsule or edge. Intraprostatic seed placement, without extraprostatic placement, would then likely result in lower rates of seed migration. Technical factors, including prostate mobility, seed tracking at implantation, degradation of the TRUS image, and operator error limit such precise

placement of all seeds. In a study by Yu *et al.* (30), it was noted that seed placement may occasionally vary by up to 1 cm from the intended position. In a related study (21), supplemental implantation in a prostate phantom on a "mock" cold implant was examined. Seed placement accuracy under idealized conditions with an experienced practitioner using a Mick applicator was determined. Seed placement accuracy as determined by all 41 supplemental seeds implanted ranged from 0 to 7.5 mm (mean ± standard deviation 2.3 ± 2.3 mm). Roberson *et al.* (22) found similar source placement error, with an average displacement of 4.6 mm. Such findings suggest that exclusive intraprostatic seed placement may not approach the accuracy desired to ensure complete treatment of a 3–5-mm periprostatic margin and planning target volume.

Evaluation of the preimplant TRUS-based plans revealed a rate of planned extraprostatic seed placement of 39% and an observed rate of placement of 31% by postimplant CT. Another seed placement definition, termed "peripherally placed," incorporates those seeds that are on the "line" of the contoured prostate, in addition to the seeds placed in extraprostatic locations. This latter definition is meant to account for seeds that are at the prostatic margin and may be more prone to migration than just those that are placed in extraprostatic locations. Furthermore, this definition accounts for the uncertainty in prostate segmentation whereby seeds judged to be at the prostate margin are actually in extraprostatic locations. To our knowledge, no other study, other than that of Merrick *et al.* (7), has reported either of these values, but comparisons between studies might be difficult because of the known rates of interobserver and intraobserver variability in post-TIPPB prostate contouring (31). Nevertheless, Merrick *et al.* (7) reported a rate of 41.3% extraprostatic seed placement, comparable to the rate of 39% reported in our study. Their study did not, however, find a correlation with extraprostatic seed placement and embolization; otherwise, their findings are consistent with many of those described in the present study.

It is remarkable that the planned extraprostatic placement of seeds as determined by preimplant TRUS correlated with seed migration and extraprostatic seed placement as determined by postimplant CT scanning did not. This finding may be attributable to differences in reproducibility and variability of preimplant TRUS and post-TIPPB CT imaging in segmentation of the prostate such that the preplan more accurately reflects extraprostatic seed placement. Although no recent studies directly comparing the reproducibility of preimplant TRUS with postimplant CT have been published, several studies have demonstrated that observer variability in postimplant CT segmentation is significant. In a study by Dubois *et al.* (31), interobserver and intraobserver variabilities of postimplant CT and MRI were measured and revealed that a difference of 5 mm routinely occurs in establishing prostate dimensions. Lee *et al.* (32) and Al-Qaisieh *et al.* (33) have reported that interobserver variability in postimplant prostate segmentation on CT images resulted in differences that were statistically significant with respect to predicted dosimetry. In detailed studies by Narayana *et al.* (34, 35), difficulties and differences in registering TRUS and CT for treatment planning related to TIPPB were evident. In contrast, Sech *et al.* (36) have demonstrated relatively good interexaminer reliability of TRUS prostate volume estimation using a prolate ellipsoid calculation. Furthermore, Tong *et al.* (37) have shown that step-section TRUS planimetry similar to that used in TIPPB planning has less variability in prostate volume determination than the ellipsoid method.

Patients at our institution are counseled before TIPPB that seed migration to the chest and other locations may occur. Although no untoward effects from seed migration have been observed, reducing the rate of migration after TIPPB nonetheless seems an intrinsically worthwhile endeavor. One method of reducing seed embolization is to use seeds that are packaged in absorbable suture material (10). Tapen *et al.* studied 289 consecutive patients who underwent TIPPB with the use of sutured seeds (n = 143) placed at the periphery or with loose seeds only (n = 146). The rate of seed migration in those patients with sutured seeds was 0.7% and for those with loose seeds was 11%. In their study, the postimplant CXRs were performed on the day after the procedure, so that the rate of longer term seed migration from sutured seeds may have been greater, as has been noted by Merrick *et al.* (7). Nonetheless, Tapen *et al.* (10) demonstrated a clear advantage in reducing seed migration with use of seeds in absorbable suture material. A delay in the timing of seed migration, if it is to occur, may have favorable dosimetric consequences compared with immediate seed migration. Similarly, Merrick *et al.* (7) found that the proportion of Vicryl suture-encapsulated seeds implanted influenced the rate of seed migration. Histopathologic examination of salvage prostatectomies after TIPPB failure has demonstrated that a fibrous capsule may form around the seeds after a period (14). Such observations are consistent with those described in reports on radiation pathology (38) and provide an explanation for the relative "fixity" of seeds embedded in Vicryl suture material after the suture material has been absorbed. The use of seeds in Vicryl suture material may, therefore, be considered if significant extraprostatic seed placement is contemplated in the planning process, because its use may reduce seed migration.

CONCLUSION

The number of loose seeds placed in extraprostatic locations as per the TRUS preplan correlated with an increased likelihood of seed migration to the thorax. This finding is consistent with observations made with fluoroscopy during TIPPB. Although a substantial proportion of patients had seed migration to the thorax, the small proportion of implanted seeds that migrated (≤1%) is not likely to have adverse dosimetric or patient health consequences. Until the dosimetric affects of peripheral seed loss are quantified, attention to the proportion of seeds planned for extraprostatic placement appears warranted when using a free seed approach.

REFERENCES

1. Jemal A, Murray T, Samuels A, *et al.* Cancer statistics, 2003. *CA Cancer J Clin* 2003;53:5–26.
2. Prestidge BR. Radioisotopic implantation for carcinoma of the prostate: Does it work better than it used to? *Semin Radiat Oncol* 1998;8:124–131.
3. Hempel M, Bruggmoser G, Wannenmacher M. [A rare complication of interstitial therapy with iodine-125 seeds: Embolization of a seed into the lung]. *Strahlenther Onkol* 1988;164: 531–532.
4. Steinfeld AD, Donahue BR, Plaine L. Pulmonary embolization of iodine-125 seeds following prostate implantation. *Urology* 1991;37:149–150.
5. Gupta S, Nag S, Gupta J. Pulmonary embolization of permanently implanted radioactive iodine-125 seeds. *Endocurie Hypertherm Oncol* 1993;9:27–31.
6. Huttner S, Lengsfeld M, Scholz H. [A rare route for the loss of a 125-iodine seed after the interstitial therapy of prostatic carcinoma]. *Urol A* 1992;31:96–97.
7. Merrick GS, Butler WM, Dorsey AT, *et al.* Seed fixity in the prostate/periprostatic region following brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;46:215–220.
8. Nag S. Principles and practice of brachytherapy. Armonk, NY: Futura Publishing; 1997.
9. Nag S, Scaperoth DD, Badalament R, *et al.* Transperineal palladium 103 prostate brachytherapy: Analysis of morbidity and seed migration. *Urology* 1995;45:87–92.
10. Tapen EM, Blasko JC, Grimm PD, *et al.* Reduction of radioactive seed embolization to the lung following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998;42:1063–1067.
11. Sommerkamp H, Rupprecht M, Wannenmacher M. Seed loss in interstitial radiotherapy of prostatic carcinoma with I-125. *Int J Radiat Oncol Biol Phys* 1988;14:389–392.
12. Grimm PD, Blasko JC, Ragde H. Migration of iodine-125 and palladium-103 seeds to the lung after transperineal brachytherapy for prostate cancer. *Endocurie Hypertherm Oncol* 2000;9:50.
13. Older R, Snyder B, Krupski TL, Glembocki DJ, Gillenwater JY. Radioactive implant migration in patients treated for localized prostate cancer with interstitial brachytherapy. *J Urol* 2001;165:1590–1592.
14. Davis BJ, Pfeifer EA, Wilson TM, *et al.* Prostate brachytherapy seed migration to the right ventricle found at autopsy following acute cardiac dysrhythmia. *J Urol* 2000;164:1661.
15. Davis BJ, Bresnahan JF, Stafford SL, *et al.* Prostate brachytherapy seed migration to a coronary artery found during angiography. *J Urol* 2002;168:1103.
16. Stock RG, Stone NN, Tabert A, *et al.* A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–108.
17. Narayana V, Roberson PL, Winfield RJ, *et al.* Optimal placement of radioisotopes for permanent prostate implants. *Radiology* 1996;199:457–460.
18. Nag S, Beyer DC, Friedland J, *et al.* American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 1999;46:789–799.
19. Davis BJ, Pisansky TM, Wilson TM, *et al.* The radial distance of extraprostatic extension of prostate cancer: Implications for prostate brachytherapy. *Cancer* 1999;85:2630–2637.
20. Sohayda C, Kupelian PA, Levin HS, *et al.* Extent of extracapsular extension in localized prostate cancer. *Urology* 2000; 55:382–386.
21. Davis BJ, Herman MG, LaJoie WN, *et al.* Supplemental implantation for suboptimal permanent prostate brachytherapy: A prostate phantom study. *Radiother Oncol* 2000;55S: 91–92.
22. Roberson PL, Narayana V, McShan DL, *et al.* Source placement error for permanent implant of the prostate. *Med Phys* 1997;24:251–257.
23. Grado GL, Larson TR, Balch CS, *et al.* Actuarial disease-free survival after prostate cancer brachytherapy using interactive techniques with biplane ultrasound and fluoroscopic guidance. *Int J Radiat Oncol Biol Phys* 1998;42:289–298.
24. Nag S, Bice W, DeWyngaert K, *et al.* The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2000;46:221–230.
25. Reiner WG, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. *J Urol* 1979;121:198–200.
26. Ragde H, Balsko JC, Grimm PD, *et al.* Interstitial iodine-125 radiation without adjuvant therapy in the treatment of clinically localized prostate carcinoma. *Cancer* 1997;80:442–453.
27. Davis BJ, Haddock MG, Wilson TM, *et al.* Treatment of extraprostatic cancer in clinically organ-confined prostate cancer by permanent interstitial brachytherapy: Is extraprostatic seed placement necessary? *Tech Urol* 2000;6:70–77.
28. Prete JJ, Prestidge BR, Bice WS, *et al.* A survey of physics and dosimetry practice of permanent prostate brachytherapy in the United States. *Int J Radiat Oncol Biol Phys* 1998;40:1001–1005.
29. Butzbach D, Waterman FM, Dicker AP. Can extraprostatic extension be treated by prostate brachytherapy? An analysis based on postimplant dosimetry. *Int J Radiat Oncol Biol Phys* 2001;51:1196–1199.
30. Yu Y, Waterman FM, Suntharalingam N, *et al.* Limitations of the minimum peripheral dose as a parameter for dose specification in permanent ^{125}I prostate implants. *Int J Radiat Oncol Biol Phys* 1996;34:717–725.
31. Dubois DF, Prestidge BR, Hotchkiss LA, *et al.* Intraobserver and interobserver variability of MR imaging- and CT-derived prostate volumes after transperineal interstitial permanent prostate brachytherapy. *Radiology* 1998;207:785–789.
32. Lee WR, Roach M III, Michalski J, *et al.* Interobserver variability leads to significant differences in quantifiers of prostate implant adequacy. *Int J Radiat Oncol Biol Phys* 2002;54:457–461.
33. Al-Qaisieh B, Ash D, Bottomley DM, *et al.* Impact of prostate volume evaluation by different observers on CT-based postimplant dosimetry. *Radiother Oncol* 2002;62:267–273.
34. Narayana V, Roberson PL, Winfield RJ, *et al.* Impact of ultrasound and computed tomography prostate volume registration on evaluation of permanent prostate implants. *Int J Radiat Oncol Biol Phys* 1997;39:341–346.
35. Narayana V, Roberson PL, Pu AT, *et al.* Impact of differences in ultrasound and computed tomography volumes on treatment planning of permanent prostate implants. *Int J Radiat Oncol Biol Phys* 1997;37:1181–1185.
36. Sech S, Montoya J, Girman CJ, *et al.* Interexaminer reliability of transrectal ultrasound for estimating prostate volume. *J Urol* 2001;166:125–129.
37. Tong S, Cardinal HN, McLoughlin RF, *et al.* Intra- and inter-observer variability and reliability of prostate volume measurement via two-dimensional and three-dimensional ultrasound imaging. *Ultrasound Med Biol* 1998;24:673–681.
38. Fajardo LF. Basic mechanisms and general morphology of radiation injury. *Semin Roentgenol* 1993;28:297–302.

ATTACHMENT 5

ELSEVIER

Brachytherapy 3 (2004) 136–140

BRACHYTHERAPY

Transperineal TRUS-guided prostate brachytherapy using loose seeds versus RAPIDStrand: A dosimetric analysis

Humberto M. Fagundes[1,*], Richard J. Keys[1], Mary F. Wojcik[1], Marsha A. Radden[1], Carol G. Bertelsman[1], William A. Cavanagh[2]

[1]*Department of Radiation Oncology, Missouri Baptist Medical Center, St. Louis, MO*
[2]*The Haakon Ragde Foundation for Advanced Cancer Studies, Seattle, WA*

ABSTRACT

PURPOSE: An analysis of the effect of stranded ^{125}I and loose (predominantly ^{103}Pd) sources on dosimetric outcomes of brachytherapy of the prostate.

METHODS AND MATERIALS: Between September 1998 and December 2003, 473 patients were treated with brachytherapy for biopsy-proven carcinoma of the prostate. Of these, 337 (71%) procedures were performed using free seeds placed with a Mick applicator. Beginning in April 2002, a program of stranded ^{125}I sources (RAPIDStrand) was implemented; 136 (29%) patients were treated via this approach. Dosimetric variables were collected, as were events of urinary retention.

RESULTS: Mean V100 values for the stranded ^{125}I approach were greater than those for free seeds ($p < 0.0005$), whether ^{125}I or ^{103}Pd ($p < 0.005$). Use of the strand was the most significant determinant of V100 of all variables examined. The stranded ^{125}I approach was also associated with higher mean D90 values and lower V150-urethral doses.

CONCLUSIONS: Use of stranded ^{125}I was associated with superior dosimetric outcomes in this group of patients.

Keywords: Prostate cancer; Brachytherapy; Dosimetry; V100; D90

Introduction

Prostate cancer is the most commonly diagnosed malignancy in American men, with an estimated 220,900 new cases in 2003 (1). Since the introduction of PSA screening, a growing number of patients will be diagnosed with organ-confined disease (2). The well-established treatment options for patients with early disease include radical prostatectomy, external beam radiation, or prostate brachytherapy (3). In the absence of a prospective randomized trial, retrospective studies have shown these therapies to provide comparable cure rates (4–11).

Transperineal prostate brachytherapy is a complex procedure that can be performed via a number of different approaches. This variety in technique arises from several factors, including the method of seed delivery (applicator or pre-loaded needle), the nature of implanted sources (individual, stranded, linked), and the planned distribution of the radiation dose. Several seed delivery techniques and dosimetric philosophies are currently described in the literature (12–25).

Our program started in 1998, using a technique employing loose seeds delivered with the Mick applicator (Mick Nuclear, Bronx, NY). In March of 2002, we modified our technique to employ suture-embedded radioactive sources (RAPIDStrand; Oncura, Plymouth Meeting, PA) delivered by pre-loaded needles using the Utrecht University method described by Battermann *et al.* (25). The objective of this study is a comparison of the postprocedure dosimetric outcomes resulting from the two distinct approaches.

Methods and materials

Our ultrasound-guided transperineal prostate brachytherapy program began in September 1998. All cases involved preplanned methodology, where a transrectal ultrasound

Received 9 December 2003; received in revised form 28 May 2004; accepted 28 May 2004.

* Corresponding author. Department of Radiation Oncology, Missouri Baptist Medical Center, 3015 North Ballas Road, St. Louis, MO 63131. Tel.: +1-314-996-5157; fax: +1-314-996-5398.

E-mail address: hmf8604@bjc.org (H.M. Fagundes).

1538-4721/04/$ – see front matter
doi:10.1016/j.brachy.2004.05.006

(TRUS) volume study serves as the basis for a treatment plan, which is carried out in the operating room.

A total of 473 patients with localized prostate cancer were treated between September 1998 and December 2002.

Technique 1

The technique used from September 1998 through March 2002 employed loose seeds placed with a Mick applicator (26, 27). Three hundred thirty-seven patients were treated with this technique. Of 337 patients, 28 (8%) received loose ^{125}I (0.32 mCi/seed, 0.425 U) whereas 309 (92%) patients received ^{103}Pd [NIST 99, 2.15 U (28)]. The prescription dose was 145 Gy for ^{125}I patients treated with monotherapy and 120 Gy when combined with external beam radiation. Prescription doses for ^{103}Pd patients were 125 Gy (pre-NIST 99, 115 Gy) for monotherapy and 100 Gy (pre-NIST 99, 90 Gy) for the combined modality.

Technique 2

Beginning in April 2002, we changed our technique to employ ^{125}I RAPIDStrand as described by Battermann (25). RAPIDStrand consists of ^{125}I sources embedded in a dried vicryl suture material. Approximately 80–85% of the seeds placed in the prostate were stranded, while 15–20% were placed as loose seeds, primarily to cover the base and apex around the urethra. The sources consisted of 0.33/0.34 mCi, 0.425 U ^{125}I RAPIDStrand for both monotherapy and combined modality. One hundred thirty-six patients were treated by this technique. Planned doses were identical to that of the earlier, free seed ^{125}I cases.

In all cases a peripherally weighted plan was used, in which 75–80% of seeds were placed in the periphery of the prostate gland. The clinical target volume (CTV) included the prostate gland as defined by the TRUS volume study images and the planning target volume (PTV) included a 5 mm margin around the CTV with the exception of the posterior aspect of the prostate, where the margin was minimal.

Both techniques were similar with regard to the surgical implant. On the day of the implant patients were brought into the operating room and placed either under general or spinal anesthesia. Patients were positioned in the lithotomy position and the rectum was suctioned. The perineum was scrubbed with betadine and a Foley catheter was placed with 50 cc contrast instilled into the bladder. The Foley was clamped and a C-arm X-ray unit was positioned over the pelvis. The perineum was dried and a scrotal drape was attached. A TRUS probe was inserted into the rectum and attached to the stand and stepping unit along with the template. Once the images reproduced the original volume study images, that is, aligning the prostate gland with the previous prostate volume study images, insertion of sources according to the pre-plan commenced. Extra seeds were placed at the end of the procedure at the discretion of the radiation oncologist. The Foley catheter remained in place until the completion of a CT scan either the same day or the morning following the procedure. As recommended by the American Brachytherapy Society (29), postimplant dosimetric parameters were quantified including V100, V150 prostate, V150 urethra, and D90.

Differences between the dosimetric parameters using loose seeds and RAPIDStrand were evaluated using a general linear model method (GLM; SPSS Inc., Chicago, IL), specifically a linear regression analysis solving for V100.

Results

Patient characteristics are outlined in Table 1. Given the relatively short follow-up interval, disease-free and overall survival data will not be addressed in this article.

Dosimetric outcomes as determined by 24-h CT-based postplan analysis are listed in Table 2. The observed V100 was significantly greater for the ^{125}I RAPIDStrand patients (mean, 92.5%; n = 136) than for the loose seed patients (mean, 88.4%; n = 336), $p < 0.005$ by independent samples t-test (Fig. 1).

The mean V100 for RAPIDStrand (92.5%) was significantly greater than both loose ^{125}I (78.8%) and loose ^{103}Pd (89.3%) seeds, $p < 0.005$ by F-test (Fig. 2).

Linear regression analysis solving for V100 using strand versus no strand, isotope (^{125}I versus ^{103}Pd), and type of therapy (implant combined with external beam versus implant monotherapy) revealed RAPIDStrand as the most powerful determinant of V100 in this series ($p < 0.005$, partial $h^2 = 0.12$, Table 3). Preimplant prostate volume, administration of antiandrogen therapy, and age were included in the regression and found to be insignificant.

The mean D90 for RAPIDStrand cases was significantly greater than that of ^{103}Pd free seed cases, whereas the mean V150-prostate and V150-urethra were lower (Table 2). No data on these parameters was available for the ^{125}I free seed cases.

Table 1
Patient characteristics

Presenting serum PSA	n (%)	Gleason sum	n (%)
0–9.9 ng/ml	409 (86)	2–4	3 (1)
10–19.9 ng/ml	48 (10)	5–6	322 (68)
>20 ng/ml	13 (3)	7	126 (27)
none	3 (1)	8–10	19 (4)
		none	3 (1)
Clinical stage			**n%**
T1a/b			1 (–)
T1c			257 (54)
T2a			176 (37)
T2b			17 (4)
T2c			10 (2)
T3a			4 (1)
none			8 (2)

Table 2
Dosimetric parameters by treatment type

	n	Mean V100 (SD)	Mean D90[1] (SD)	Mean V150 (SD)	Mean V150-U (SD)
Free ^{103}pd	309	89.3 (7.7)	103.4[2] (17.2)	59.8 (12.3)	9.8 (15.0)
Free ^{125}I	28	78.8 (12.9)	not done	not done	not done
RAPID Strand ^{125}I	136	92.5[3] (5.9)	108.8[3] (13.0)	46.5[3] (12.1)	3.6[3] (8.6)

[1] Normalized to prescription dose.
[2] n = 284.
[3] $p < 0.005$ vs. other treatment(s).

The rate of retention for free ^{125}I was 1/27 (3.6%), for free ^{103}Pd 30/309 (9.7%), and for RAPIDStrand 4/136 (2.9%). These differences were significant (exact p = 0.01).

Discussion

Several authors have compared postimplant dosimetry using loose versus suture-embedded seeds. Battermann (25) reported the Utrecht University experience using loose and stranded ^{125}I. Based on a series of 249 patients, he noted an increase in mean coverage from 55–68% of the prostate volume with loose seeds to 90% with RAPIDStrand. In addition, the reported seed migration dropped from 10% to 1–3% following the implementation of stranded seeds.

Lee *et al.* (17) used loose sources for 3 years before changing to embedded ^{125}I seeds. Patients treated with suture-embedded seeds were found to have significantly improved dosimetric coverage of the prostate gland. In that series, the observed mean V100 was 94.1% versus 86.54% for the patients treated with loose seeds ($p < 0.001$).

Fagundes *et al.* (30) reported dosimetric results from Porto Alegre, Brazil using the Mick applicator with loose ^{125}I and RAPIDStrand. They noted an improvement in the V100 from 82.8% with loose seeds to 93.6% with RAPIDStrand.

The present series revealed a statistically significant improvement in the dosimetry when RAPIDStrand was used. The observed V100 improved from 88.4% to 92.5% based on postimplant CT scan done within 24 h following implementation of RAPIDStrand. Since this series includes patients treated by free ^{125}I, free ^{103}Pd, and stranded ^{125}I, we are able to show a greater V100 for RAPIDStrand cases than both free ^{103}Pd and free ^{125}I cases. Likewise, upon regression analysis, while both isotope and implant dose (for boost or primary therapy) are significant factors for V100, the use of RAPIDStrand retains significance as a predictor in the final model (Table 3).

Patients implanted by the RAPIDStrand technique also experienced less acute urinary retention: 8.9% with loose seeds versus 2.9% with RAPIDStrand (p = 0.01). This decline in urinary retention correlated with a lower V150 urethra, 9.7% versus 2.8%. However, given the lack of detailed dosimetry data for the early loose ^{125}I cases, we are unable to attribute this difference unequivocally to RAPIDStrand, as isotope selection may play an important role. The same is true of D90, V150 prostate, and V150 urethra,

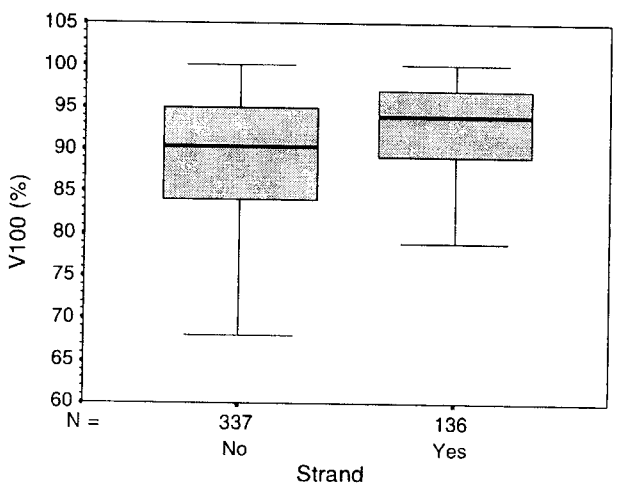


Fig. 1. Boxplot of V100 by strand vs. no strand.

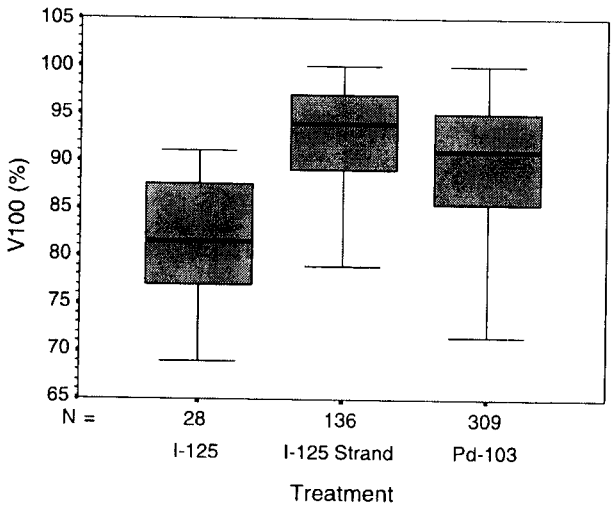


Fig. 2. Boxplot of V100 by isotope and strand.

Table 3
Best fit linear regression for V100

	P	Effect size[1]
^{100}Pd vs. ^{125}I	<0.005	0.08
Primary vs. boost	<0.005	0.03
RAPID Strand vs. loose	<0.005	0.12
Hormone treatment	0.4	n/a
Pre-implant prostate volume	0.9	n/a
Age	0.5	n/a

[1] Partial η^2.

where significant differences were also noted (Table 2). These data support the notion of improved dose homogeneity within the prostate gland with RAPIDStrand over free seed techniques, although isotope selection cannot be ruled out as a determinant.

Other authors have compared ^{103}Pd versus ^{125}I (14, 31). Even though it has been theorized that ^{103}Pd might be a better choice for high-grade lesions and ^{125}I for lower grade ones, Wallner *et al.* (31) and Cha *et al.* (14) observed similar biochemical control rates for the two isotopes. Fuller and Koziol (32) evaluated several factors using V100 as an indicator of implant quality. They found stranded source type and ^{125}I to be significant predictors of a higher V100, resulting in a better implant.

An additional factor not well described in the literature is the use of extra seeds used to fill in "cold spots" at the completion of the implant. In the loose seed era, we customarily used extra seeds in about 10–15% of the cases based on cold spots on fluoroscopy due to intraprostatic seed migration as well as peripheral seeds migrating away from the prostate gland. In the RAPIDStrand era, it is unusual for us to use added seeds since we have rarely observed seed migration within or outside the prostate (less than 2%).

It is possible that a "learning curve" contributed to the differences in outcome, especially with reference to free ^{125}I, as improved outcomes mirrored the temporal sequence of free ^{125}I, free ^{103}Pd, and RAPIDStrand ^{125}I techniques.

In summary, using V100 as an indicator of implant quality for our patients, this RAPIDStrand approach demonstrates an advantage over the standard, free-seed method previously used. This technique has also been associated with a lower urinary retention rate, although isotope selection may also play an important role.

References

[1] American Cancer Society. Cancer facts and figures. Atlanta: American Cancer Society; 2003.

[2] Amling CL, Blute ML, Lerner SE, *et al.* Influence of prostate-specific antigen testing on the spectrum of patients with prostate cancer undergoing radical prostatectomy at a large referral practice. *Mayo Clin Proc* 1998;73:401–406.

[3] Bahnson RR, Hanks GE, Huben RP, *et al.* NCCN Practice Guidelines for Prostate Cancer. *Oncology (Huntington)* 2000;14(11A):111–119.

[4] Blasko JC, Grimm PD, Sylvester JE, *et al.* Palladium-103 brachytherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2000;46: 839–850.

[5] Catalona WJ, Smith DS. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: Intermediate-term results. *J Urol* 1998;160:2428–2434.

[6] Ragde H, Grado GL, Nadir BS. Brachytherapy for clinically localized prostate cancer: Thirteen-year disease-free survival of 769 consecutive prostate cancer patients treated with permanent implants alone. *Arch Esp Urol* 2001;54:739–747.

[7] Grimm PD, Blasko JC, Sylvester JE, *et al.* Ten-year biochemical (prostate-specific antigen) control of prostate cancer with ^{125}I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51:31–40.

[8] Han M, Partin AW, Piantadosi S, *et al.* Era-specific biochemical recurrence-free survival following radical prostatectomy for clinically localized prostate cancer. *J Urol* 2001;166:416–419.

[9] Sharkey J, Cantor A, Solc Z, *et al.* Brachytherapy versus radical prostatectomy in patients with clinically localized prostate cancer. *Curr Urol Rep* 2002;3:250–257.

[10] Wallner K, Roy J, Harrison L. Tumor control and morbidity following transperineal ^{125}I implantation for stage T1/T2 prostatic carcinoma. *J Clin Oncol* 1996;14:449–453.

[11] Zelefsky MJ, Leibel SA, Gaudin PB, *et al.* Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;41:491–500.

[12] Bice WS Jr, Prestidge BR, Grimm PD, *et al.* Centralized multi-institutional postimplant analysis for interstitial prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998;41:921–927.

[13] Butler WM, Merrick GS, Dorsey AT, *et al.* Comparison of dose length, area, and volume histograms as quantifiers of urethral dose in prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;48:1575–1582.

[14] Cha CM, Potters L, Ashley R, *et al.* Isotope selection for patients undergoing prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;45:391–395.

[15] Horwitz EM, Mitra RK, Uzzo RG, *et al.* Impact of target volume coverage with Radiation Therapy Oncology Group (RTOG) 98-05 guidelines for transrectal ultrasound guided permanent ^{125}I prostate implants. *Radiother Oncol* 2003;66:173–179.

[16] Lee WR, deGuzman AF, Bare RL, *et al.* Postimplant analysis of transperineal interstitial permanent prostate brachytherapy: Evidence for a learning curve in the first year at a single institution. *Int J Radiat Oncol Biol Phys* 2000;46:83–88.

[17] Lee WR, deGuzman AF, Tomlinson SK, *et al.* Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy. *Radiother Oncol* 2002;65:123–127.

[18] Merrick GS, Butler WM, Lief JH, *et al.* Temporal resolution of urinary morbidity following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;47:121–128.

[19] Merrick GS, Butler WM, Dorsey AT, *et al.* Potential role of various dosimetric quality indicators in prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;44:717–724.

[20] Merrick GS, Butler WM, Dorsey AT, *et al.* Prostatic conformal brachytherapy: ^{125}I/^{103}Pd postoperative dosimetric analysis. *Radiat Oncol Investig* 1997;5:305–313.

[21] Merrick GS, Butler WM, Dorsey AT, *et al.* Influence of timing on the dosimetric analysis of transperineal ultrasound-guided, prostatic conformal brachytherapy. *Radiat Oncol Investig* 1998;6:182–190.

[22] Ove R, Wallner K, Badiozamani K, *et al.* Standardization of prostate brachytherapy treatment plans. *Int J Radiat Oncol Biol Phys* 2001; 50:257–263.

[23] Stock RG, Stone NN, Tabert A, *et al.* A dose–response study for ^{125}I prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–108.

[24] Potters L, Huang D, Fearn P, *et al.* The effect of isotope selection on the prostate-specific antigen response in patients treated with permanent prostate brachytherapy. *Brachytherapy* 2003;2:26–31.

[25] Battermann JJ. I-125 implantation for localized prostate cancer: The Utrecht University experience. *Radiother Oncol* 2000;57:269–272.

[26] Grado GL, Larson TR, Balch CS, *et al*. Actuarial disease-free survival after prostate cancer brachytherapy using interactive techniques with biplane ultrasound and fluoroscopic guidance. *Int J Radiat Oncol Biol Phys* 1998;42:289–298.

[27] Sharkey J, Chovnick SD, Behar RJ, *et al*. Evolution of techniques for ultrasound-guided ^{103}Pd brachytherapy in 950 patients with prostate cancer. *Tech Urol* 2000;6:128–134.

[28] Williamson JF, Coursey BM. Recommendations of the American Association of Physicists in Medicine on ^{103}Pd interstitial source calibration and dosimetry: Implications for dose specification and prescription. *Med Phys* 2000;27:634–642.

[29] Nag S, Beyer D, Friedland J, *et al*. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 1999;44:789–799.

[30] Fagundes MA, Leick M, Sabrito C, *et al*. Permanent prostate gland seed implant: A dosimetry report of the Porto Alegre, Brazil experience comparing two different brachytherapy techniques. *Radiother Oncol* 2003;66(Suppl. 95):S33.

[31] Wallner K, Merrick G, True L, *et al*. I-125 versus Pd-103 for low-risk prostate cancer: Morbidity outcomes from a prospective randomized multicenter trial. *Cancer J* 2002;8:67–73.

[32] Fuller DB, Koziol JA. Prostate brachytherapy seed migration and dosimetry: Analysis of potential predictive factors. *Brachytherapy* 2003;2:47.

ATTACHMENT 6

Calculated and measured brachytherapy dosimetry parameters in water for the Xoft AXXENT X-Ray source: An electronic brachytherapy source[a)]

Mark J. Rivard[b)]
Department of Radiation Oncology, Tufts-New England Medical Center, Boston, Massachusetts 02111

Stephen D. Davis and Larry A. DeWerd
Medical Radiation Research Center, University of Wisconsin, Madison, Wisconsin 53706

Thomas W. Rusch and Steve Axelrod
Xoft, Inc., Fremont, California 94538

A new x-ray source, the model S700 AXXENT™ X-Ray Source (Source), has been developed by Xoft Inc. for electronic brachytherapy. Unlike brachytherapy sources containing radionuclides, this Source may be turned on and off at will and may be operated at variable currents and voltages to change the dose rate and penetration properties. The in-water dosimetry parameters for this electronic brachytherapy source have been determined from measurements and calculations at 40, 45, and 50 kV settings. Monte Carlo simulations of radiation transport utilized the MCNP5 code and the EPDL97-based mcplib04 cross-section library. Inter-tube consistency was assessed for twenty different Sources, measured with a PTW 34013 ionization chamber. As the Source is intended to be used for a maximum of 10 treatment fractions, tube stability was also assessed. Photon spectra were measured using a high-purity germanium (HPGe) detector, and calculated using MCNP. Parameters used in the 2-D brachytherapy dosimetry formalism were determined. While the Source was characterized as a point due to the small anode size, < 1 mm, use of the 1-D brachytherapy dosimetry formalism is not recommended due to polar anisotropy. Consequently, 1-D brachytherapy dosimetry parameters were not sought. Calculated point-source model radial dose functions at $g_P(5)$ were 0.20, 0.24, and 0.29 for the 40, 45, and 50 kV voltage settings, respectively. For $1 < r < 7$ cm, measured point-source model radial dose functions were typically within 4% of calculated results. Calculated values for $F(r,\theta)$ for all operating voltages were within 15% of unity along the distal end ($\theta = 0°$), and ranged from F(1 cm, 160°) = 0.2 to F(15 cm, 175°) = 0.4 towards the catheter proximal end. For all three operating voltages using the PTW chamber, measured dependence of output as a function of azimuthal angle, ψ, was typically on average ± 3% for $0° \leq \psi \leq 360°$. Excluding an energy response function, measurements of normalized photon energy spectra were made for three operating voltages, and were typically within 2% agreement with the normalized Monte Carlo calculated spectra. In general, the model S700 Source exhibited depth dose behavior similar to low-energy photon-emitting LDR sources ^{125}I and ^{103}Pd, yet with capability for variable and much higher dose rates and subsequently adjustable penetration capabilities. This paper presents the calculated and measured in-water brachytherapy dosimetry parameters for the model S700 Source at the aforementioned three operating voltages.

Key words: electronic brachytherapy, TG-43, brachytherapy dosimetry

I. INTRODUCTION

Recently, small x-ray tubes have been developed that offer the prospect of electronic brachytherapy. Xoft Inc. has developed a miniature x-ray brachytherapy source called the Xoft AXXENT™ X-Ray Source (Source).[1-5] The model S700 Source consists of a disposable, micro-miniature x-ray tube (**Fig. 1**) integrated into a cooled, flexible, disposable sheath which is directly attached to a treatment control console (**Fig. 2**). Water circulating within the cooling sheath having intimate contact with the anode allows a higher power dissipation and higher dose rate, without thermal damage to the Source, surrounding probe structures, or the patient. If the cooling water supply is interrupted, the treatment control console will immediately shut off the operating voltage. Furthermore, if the tube should overheat, the Source will electronically short and terminate the operating voltage and radiation output.

The Source is capable of operating voltages ranging from 20 kV to 50 kV. This range provides photons with maximum energy less than 50 keV which negates shielding concerns required by a ^{192}Ir source used for high dose rate (HDR) brachytherapy. The Source current and photon beam intensity may be modulated to approximate the penetration and/or dose rate characteristics of clinically suitable radionuclides such as HDR ^{192}Ir, LDR ^{125}I, and LDR ^{103}Pd. Therefore, an increased level of dose conformity is possible. At an operating voltage of 50 kV, the Source can produce air kerma strengths ranging from 1,400 Gy cm^2 h^{-1} with a tube current of 300 μA (approximately thrice that of a 10 Ci HDR ^{192}Ir source) down to 4.7 Gy cm^2 h^{-1} at 1 μA. Like conventional HDR remote afterloading brachytherapy sources using radionuclides attached to delivery drive wires, the Source can be positioned within the patient at multiple dwell positions for providing highly-conformal radiotherapy delivery. This method of operation was approved by the FDA in December 2005. Initial clinical applications will operate at fixed voltage and currents, 50 kV and 300 μA for 15 W of power, with a tube design lifetime of 2.5 hours for multi-fraction treatments of an entire therapy course.

Another miniature x-ray source has been used for interstitial and intracavitary radiation therapy, the photon radiosurgery system (PRS) or INTRABEAM™ System developed by the Photoelectron Corporation, and now owned and marketed by Carl Zeiss, Inc. in North America. This device has been used intraoperatively for the irradiation of intracranial metastases and irradiation of the tumor bed following breast-conserving surgery.[6-8] X-rays are generated in the PRS by a 50 keV electron beam focused from a conventional miniature electron gun onto the tip of a 3 mm diameter rigid drift tube.[9-11] The tip of the drift tube comprises a beryllium tube with hemispherical x-ray window coated on the inside with a thin Au target and on the outside with thin nickel and titanium nitride films for biocompatibility. The electron beam is positioned in the center of the hemispherical Be window using a static magnetic deflection system. The Zeiss device has a dose distribution that is approximately spherically-symmetrical but drops off in the proximal direction. Depth-dose data for a 25 minute treatment time using the INTRABEAM™ System at 40 μA and 50 kV were reported as 20, 5, and 1 Gy at 0.1, 1.0, and 2.7 cm, respectively, from the outer surface of a 3.5 cm diameter spherical applicator.[7] As will be shown later, the Xoft AXXENT™ Source has a near-field dose rate that is at least six times higher beyond the catheter, and a more slowly decreasing depth-dose curve in comparison to the INTRABEAM™ System. This latter feature is due in part to the higher average photon energy from the Xoft AXXENT™ Source through tube filtration of the low-energy x-rays.

This study presents in-water brachytherapy dosimetry parameters and data, calculated and measured at 40 kV, 45 kV, and 50 kV at 300 μA, needed for clinical implementation of the Source with treatment planning systems.[12-14] While not a LDR brachytherapy seed, this publication aims to provide data to satisfy, in part, the AAPM recommendations for dosimetric prerequisites and clinical implementation for posting on the joint AAPM/RPC Brachytherapy Source Registry.[15]

II. MATERIALS AND METHODS

Certain commercial equipment, instruments, materials, and software are identified in this publication in order to adequately specify the experimental and calculative procedures. Such identification does not imply recommendation or endorsement by either the authors or their respective institutions, nor does it imply that the hardware or software identified is necessarily the best available for these purposes.

A. AXXENT™ X-Ray Source

Calculations and experiments were performed to determine Source dose rate distributions in water. These dose rates were then manipulated to determine the requisite AAPM brachytherapy dosimetry parameters for subsequent use in treatment planning systems. The coordinate system was arbitrarily oriented such that $\theta = 0°$ points along the Source distal direction (z-axis), and asymmetry about the transverse-plane (x-y plane) requires treatment planning from $0° \leq \theta \leq 180°$. This orientation is the same as for the Nucletron PLATO treatment planning system, yet $\theta = 0°$ points along the Source proximal direction for the Varian BrachyVision treatment planning system.

B. Radiation transport calculations

Section V.E of the AAPM TG-43U1 report provides "Good Practice" recommendations for investigators performing Monte Carlo calculations, and that certain aspects of the calculation setup be described.[12] We endeavored to follow these recommendations. Unlike radionuclides where there are recommended photon

energy spectra such as for ^{125}I and ^{103}Pd, the Source photon energy spectra were initially unknown. In this study, Source spectra were calculated using mono-energetic electrons striking the anode surface to generate x-rays. The electrons had kinetic energies of 40 keV, 45 keV, and 50 keV, and Monte Carlo calculations were used for determining the radiological physics interactions of photons and electrons in various media. While this brachytherapy application has not been previously studied using MCNP, the code has been benchmarked with measurements for photon production due to electron bremsstrahlung on similar high-Z materials.[16-24] Photon energy spectra were calculated using the Monte Carlo N-Particle radiation transport code (version MCNP5) using the EPDL97-based cross-section libraries, particle fluence F4 tally estimator with photon energy binned at 100 eV intervals, and the mass-attenuation coefficients of Seltzer used in the MCNP5 F6 tally.[25-30] Unlike version 4C of MCNP which is subject to dosimetric errors due to inaccuracies in the default cross-section libraries, MCNP5 uses the latest set of libraries, EPDL97-based mcplib04.[31-33] Calculations typically required 10^9 histories to achieve sufficient statistics to discern the effects studied. This number of histories produced statistical uncertainties of 0.05% and 0.2% at 1 cm and 5 cm on the transverse plane, and 0.3% and 0.8% at 1 cm and 5 cm near the long-axes, respectively.

The Source geometry was simulated as shown in **Fig. 1**, assuming symmetry about the long axis. Components included in the model S700 simulation were the x-ray anode and substrate, wall materials, and water cooling sheath (5.3 mm outer diameter). While the internal dimensions and compositions are proprietary, the primary element producing x-rays in the anode is tungsten. The coordinate system origin was positioned at the center of the x-ray anode cone. Details of the cooling sheath were included in all calculations presented herein. Calculations were performed at Tufts University, the University of Wisconsin, and Xoft. Generally, these were done in a 20 cm radius spherical liquid water phantom with an atomic ratio of 2:1 for H:O and ρ = 0.998 g/cm^3. Data were calculated for all three operating voltages at $0° \leq \theta \leq 180°$ with 1° increments, and for $0.4 \leq r \leq 15$ cm with 0.1 cm increments. The AAPM recommends at least 5 cm of backscattering material to approximate infinite scatter conditions when determining dose rate distributions within 10 cm of low-energy photon-emitting radionuclides such as ^{125}I and ^{103}Pd.[13] This guidance has recently been substantiated over a wide range of radii and photon energies for a variety of radionuclides and monoenergetic photon-emitting sources.[34,35] More specifics on the geometry and voxel size used for calculating each set of brachytherapy dosimetry parameters are provided in the following sections.

C. Experimental measurements

Dose rate measurements were performed at Xoft using a PTW parallel plate ionization chamber (model 34013, from Freiburg, Germany) that was specifically designed for characterization of the INTRABEAM™ System. Due to its acrylic construction, radiological similarity to water at these photon energies, and small collecting volume (1.7 mm diam., 0.45 mm thick air gap), this chamber is suitable for high dose rate measurements in water. The PTW ion chamber was calibrated at PTW with traceability to the German National Laboratory (PTB in Braunschweig, Germany) over an energy range (15 kVp to 70 kVp) which bounded those examined herein for the source at 40 – 50 kV. An uncertainty (k=2) of ± 2% is reported for this energy range. The ionization chamber was within current calibration, as was the electrometer, a PTW UniDos E model. A computer running custom LabVIEW™ data acquisition and analysis software (National Instruments, Austin, TX) communicated with the electrometer via a serial port. Data was exchanged by ASCII strings, eliminating the possibility of inaccurate communications. The computer also controlled the high voltage power supply (HVPS) through National Instruments analog data acquisition cards on the PCI bus. The power supply was separately calibrated with respect to front panel displays. The LabVIEW software was then checked against the HVPS displays for accuracy. Individual readings from the electrometer were sampled at 0.5 second intervals. Typically 10 such readings were combined to yield an individual data point. Statistics were recorded, including the standard deviation of the readings, as a measure of system stability. Typically, standard deviations of the 0.5 second readings were on the order of 0.25% of the signal, even for signals as small as 0.25 pA.

Depth dose (for radial dose function), polar, and azimuthal dose rate data were acquired with a specially constructed fixture operating in a water tank. The measurement apparatus was mounted atop a steel water tank (11.0 cm high × 29.2 cm long × 29.2 cm wide) designed to be opaque to source radiation and is shown as a CAD rendering in **Fig. 3**. A SolidWater™ case, front thickness of 1.0 mm, enclosed the PTW chamber in a water tight configuration while permitting atmospheric pressure equilibration via a thin snorkel tube extending out of the water. The Source catheter entered the tank either vertically through the top or horizontally through

thin walled stainless steel tubes that ended at least 2 cm from the anode. For depth-dose measurements the Source entered the tank vertically, the chamber was positioned 90° relative to the Source long-axis then the linear stage stepped it from 1.0 cm to 7.0 cm in 0.2 cm increments. Azimuthal readings also used vertical source orientation; the detector distance was set using the linear stage then the rotary stage moved the detector from 0° to 360° in 10° steps. Polar angle measurements were made with the Source horizontal; once again the detector distance was set via the linear stage, with the rotary stage locating the detector along an arc with the Source in the center. Due to interference between detector and catheter, the extremes of the arc depended on the detector distance; at larger distances a larger angular range was possible. A two axis micrometer stage (not shown) controlled the location of the horizontal entry tube to allow for precise Source alignment to the axis of rotation.

The Source:detector distance was varied by a computer-controlled long-throw linear stage. The linear stage was mounted to a computer-interfaced rotary stage, providing angular control while maintaining the proper orientation of the detector entrance window to the Source. Stainless steel mounting fixtures, chosen for mechanical precision and compatibility with the water tank environment, were designed to be far enough from the Source and detector so as not to introduce detectable measurement errors. An identically constructed copy of the apparatus was subjected to a detailed inspection process, to validate accuracy of mechanical movement and positions. Location of the anode, which is the true source of the x-rays, depends to an extent on the cooling catheter it resides within. The cooling catheter is designed with a plastic insert at its inner end that locates the anode longitudinally and centers it, while allowing for adequate flow of water over the anode surface. Location of the cooling catheter lengthwise within the stainless steel tube establishes the anode position in the plane of the detector in azimuthal measurements, and must be accurate to within 1 mm. For polar measurements, the cooling catheter position is critical since it sets the anode position within the arc traversed by the detector. In order to mitigate effects based on the intrinsically high-sensitivity of results to Source:detector positioning, a spotting telescope with graticule was built into the side of the radiation tank. In combination with crosshair marks etched onto the SolidWater™ detector enclosure, longitudinal alignment is estimated to have an accuracy of 0.2 mm or better. Concentricity of detector rotation around the tube which guides the catheter and Source was adjusted on a lathe during assembly, and measured at time of use to be consistent at 0°, 90°, 180°, 270°, and 360° within a measurement uncertainty of ± 0.1 mm. Absolute determination of Source:detector distance involved three direct measurements, plus use of the PTW-supplied 0.30 mm offset of the model 34013 chamber front window from the front locating surface. Distance values derived in this way were consistent with expected values, producing a localization uncertainty of ± 0.2 mm. At r = 1, 2, and 3 cm, this level of localization uncertainty would be associated with dose rate uncertainties of ± 4%, 2%, and 1%, respectively.

To improve measurement statistics and evaluate consistency, all experimental results were obtained from twenty separate Sources at 50 kV (n=3 for 40 and 45 kV), and results from two complete rotations were averaged to improve measurement uncertainties of the angular distributions. Since some of the measurements were lengthy and the Sources have a finite beam life, approximately 110 Sources were used to perform the experiments described herein. The intent is for manufacturer quality control to negate the need for medical physicists to measure and validate brachytherapy dosimetry parameters, requiring only a measure of source strength preceding each treatment fraction. This approach has been approved by the U.S. FDA, and a separate publication is in preparation to evaluate the dose rate constant and provide an air kerma strength calibration.

D. Photon energy spectra

Calculated and measured photon energy spectra were determined in-air. Calculations were performed using MCNP5 and 100 eV energy bins. Measurements were performed using a CdTe solid-state detector at Xoft Inc., a high-purity germanium (HPGe) detector at the University of Wisconsin, and a HPGe detector during a research trip to the National Institute of Standards and Technology (NIST). Due to significant artifacts of K-edge photo-escape peaks from cadmium and tellurium, results from the CdTe detector are not presented. Because of improvements to the Source design since inception of this study, only recently obtained results at NIST are presented. Photon spectra were measured as a function of beam current, operating voltage, aperture, and filtration for a single Source. For consistency, only unfiltered spectra are presented. A 0.25 mm diameter tungsten aperture was used to collimate the Source photons which were measured in-air with 60 eV energy bins at a distance of 178 cm to minimize HPGe detector dead-time. Calculated and measured counts were normalized over the 23.0 to 26.0 keV range to minimize impact of characteristic x- ray peaks at the low-energy

end and decreasing photon yield at the high-energy end. Note that photons of 10 keV, 20 keV, and 30 keV are attenuated by approximately 67%, 15%, and 7% in air at 178 cm, respectively.

E. Brachytherapy dosimetry parameters

1. Point-source 2-D dosimetry formalism

The appropriate combination of the brachytherapy dosimetry parameters in a treatment planning system should provide the correct dose rate distributions to the clinical user. All of these parameters require specification of either an active length, L, or an effective length, L_{eff}. By design, the Source anode size results in $L_{eff} \leq 0.1$ cm. If one were to conservatively use $L_{eff} = 0.1$ cm, the geometry function for $r \geq 0.5$ cm using a line-source approximation would not differ from that using a point-source approximation by more than 1%. Therefore, we set $L_{eff} \equiv 0$ and used the point-source approximation with $G_P(r,\theta) = 1/r^2$ throughout this work. However, the 2-D formalism is still applicable due to polar anisotropy as will be shown later. Since recommendations in the TG-43U1 report do not explicitly include a 2-D dosimetry formalism to account for point sources, the following equation, **Eq. (1)**, is presented to depict the formalism that was used for calculating the 2-D dose rate distributions:

$$\dot{D}(r,\theta) = S_K \cdot \Lambda \cdot \left(\frac{r_0}{r}\right)^2 \cdot g_P(r) \cdot F(r,\theta). \qquad (1)$$

2. Radial dose function

Using a $1/r^2$ geometry function, dose rate data normalized to $\dot{d}(r_0, \theta_0)$ permitted calculation of $g_P(r)$ for all three operating voltages. These data are referred to as ${}_{MC}g_P(r)^{40}$, ${}_{MC}g_P(r)^{45}$, and ${}_{MC}g_P(r)^{50}$ for the 40, 45, and 50 kV voltage settings, respectively. For measurements of ${}_{PTW}g_P(r)^{40}$, ${}_{PTW}g_P(r)^{45}$, and ${}_{PTW}g_P(r)^{50}$, the PTW 34013 chamber was moved by the stage from $1.0 \leq r \leq 7.0$ cm in 0.2 cm increments for all three operating voltages. At 40, 45, and 50 kV, measurements were made with 3, 3, and 20 Sources, respectively. Because the SolidWater™ detector enclosure was thin and measurements were performed in liquid water, no medium correction factors were needed for reporting radial dose function results. At r_0, the standard deviation of measured dose rates for a given Source was < 0.3% at all three operating voltages. For all three operating voltages, the average standard deviations of measured g(3), g(5), and g(7) were 4.5%, 5.3%, and 6.3%, respectively, and did not trend as a function of operating voltage.

3. Polar angle dependence

The radial and angular ranges for calculated $F(r,\theta)$ values are given in section II.B. $F(r,\theta)$ values were measured at 2, 3, 5, and 7 cm for $-150° \lesssim \theta \lesssim +150°$ in 10° increments. These measurements were performed for all 3 operating voltages, for twenty different Sources, and then repeated. Thus, a total of 14,880 separate $F(r,\theta)$ measurements were obtained from Xoft. Data were not collected at the proximal-end at $|\theta| \gtrsim 150°$ due to interference between the detector and coolant sheath. This constraint was distance-dependent. As the origin of radiation from the Source was approximated as a point-source, readings normalized to the θ_0 reading resulted in direct measurements of $F(r,\theta)$. Reproducibility of measurements at a fixed distance and voltage was examined by comparing results at the same angle, e.g., –30° and +30° obtained during two different rotations. $F(r,\theta)$ variability amongst the twenty Sources was also examined.

4. Azimuthal angle dependence

Since the manufacturing process, and subsequently the Monte Carlo model, did not intentionally include asymmetry about the Source long-axis, no dependence of output as a function of azimuthal angle, ψ, is expected. Constancy of output as a function of azimuthal angle, ψ, was measured in 15° increments from 0° to 360°, and at radial distances of 2, 4, and 6 cm for 20 different Sources at all operating voltages. The average variation as a function of azimuthal angle was obtained. Measurement reproducibility was examined by comparing rotationally symmetric results, i.e., results at 0° were compared with results at 360°.

III. RESULTS AND DISCUSSION

A. Photon energy spectra

Fig. 4 shows the pulse-height distributions measured with the HPGe detector for a Source operating at 40, 45 and 50 kV. Note that no corrections have been made for the detector response function, including the energy-dependent detector efficiency; only the normalized counts within a given energy bin are shown. From **Fig. 4**, it is evident that the maximum photon energies, keV, match the applied operating voltage, kV. The 8, 10, and 11 keV peaks result from tungsten L-edge characteristic x-rays (tungsten is used for the anode film); the 15 keV and 17 keV peaks result from yttrium K-edge characteristic x-rays (yttrium is a constituent of the anode substrate); and the 22 keV peak results from silver K-edge characteristic x-rays (silver is a constituent of the brazing alloy). Average calculated photon energies for the Source operating in air at 40, 45, and 50 kV were 22.8, 24.7, and 26.6 keV, with average measured photon energies of 23.1, 24.9, and 26.7 keV, respectively. Agreement amongst all operating voltages and energy bins was generally within 2%; bin-to-bin measurement noise was typically 4% near 25 keV, and the MCNP statistical error was typically < 1%. Differences between measurements and calculations exceeded 20% at energies less than 12 keV, and were primarily due to the omission of multiple L-line generation by MCNP and unavailability of HPGe energy-dependent response functions correlating counts with photon energy fluence at the time of measurements. Upon examining the 40 kV Source spectra with to 40 kV INTRABEAM™ spectra published in Fig. 3 by Yanch and Harte,[11] it is evident that the higher-energy photons are comparable. Differences in lower-energy photons arise from differences in the target materials.

B. Dose rates in water at the reference position

Table I presents the measured and calculated dose rates to water at the reference position at all three operating voltages. Increases in dose rates to water for a fixed beam current as a function of operating voltage are attributed to increased conversion efficiency for increasing applied potential as is typical of bremsstrahlung radiation emission. Measurement variability amongst Sources was attributed to differing tube efficiencies resultant from variables in the manufacturing process. Also, the maximum and average measured values for dose rates to water at the reference position were typically 17% and 40% less than the Monte Carlo results. This implied that the MCNP model may have over-estimated the photon production efficiency; that the maximum tube efficiency to produce photons was 78%, 80%, and 91% of that produced by the MCNP model at 40, 45, and 50 kV, respectively; or that there was some combination of these reasons.

C. Radial dose function

Calculated and measured $g_P(r)$ for all three operating voltages are presented in **Table II**. For distances greater than r_0, $g_P(r)$ exhibit greater penetration ability as operating voltage increased. As distance increased, agreement between the two methods monotonically decreased. The disagreement could be based on artifacts of the simulations such as small differences between the actual and simulated in-water photon spectra since MCNP physics currently does not produce multiple tungsten L-edge characteristic x-rays arising from electron impact ionization. Variations in calculated g(r) results due to statistical uncertainties were typically 0.1% for all operating voltage for $r \leq 7$ cm. This disagreement could also be attributed to measurements using the PTW ionization chamber: i) a 0.2 mm positioning offset would place calculated results within the standard deviation of measured results, ii) a slight change in the response of the PTW ionization chamber because of varying photon energy at depth, or iii) non-uniform angular sensitivity to an increasing amount of scattered radiation which increases as depth increases. For measured ${}_{PTW}g_P(r)$[50] results at 2, 3, 5, and 7 cm with 20 Sources, the standard deviation (k=2) was ±7.3%, ±9.1%, ±11.7%, and ±14.2%, respectively. Regardless, the observed differences between calculated and measured g(r) results were relatively small given other differences observed in the literature for low-energy photon-emitting brachytherapy source dosimetry.[13] In **Fig. 5**, g(r) data for the Source are compared to data for conventional radionuclides such as HDR ^{192}Ir,[36] and ^{125}I (model 6711) and ^{103}Pd (model 200) from the 2004 AAPM TG-43U1 report.[13]

D. 2-D Anisotropy function

The calculated $F(r,\theta)$ data for the three operating voltages are presented in **Tables III through V**, and the measured $F(r,\theta)$ data are presented in **Table VI**. As expected due to increased average photon energy, it is evident that the anisotropy decreases with increasing operating voltage. Anisotropy is higher towards the proximal direction due to attenuation within the Source. The last three columns in **Table VI** provide a

comparison of the measured and calculated $F(r,\theta)$ data at select distances and angles. As the solid-angle weighted results at each distance illustrate, there was very good agreement between calculated and measured $F(r,\theta)$ results at all distances and for all three operating voltages. This agreement further substantiates both methodologies. Summarizing all the results in this publication, it seems that Monte Carlo methods are capable of predicting the photon energy spectra and the relative dosimetry parameters, $F(r,\theta)$ and $g(r)$, but not the absolute in-water dose rate (**Table I**).

E. Azimuthal angular dependence

For 20 Sources at 50 kV, the change in output relative to average output as a function of azimuthal angle had a range of 15.0%, 8.4%, and 6.1% at 2, 4, and 6 cm, respectively. One standard deviation of these results at the same distances was 3.4%, 2.1%, and 1.5%, respectively. Consequently, a quality control procedure has been established at Xoft to measure Sources preceding shipment to ensure that those provided for clinical use will not have large output variations as a function of azimuthal angle. An indication of stability of the entire system was obtained from the measured reproducibility of the same Source upon rotation through 360°. Here, changes of 0.2% were observed. Similar results were obtained for the other two operating voltages.

One may compare these changes in output as a function of azimuthal angle with those exhibited by radionuclides. Rivard *et al.* modeled a hypothetical ^{103}Pd source, and obtained an azimuthal angle dependence of air kerma strength having a range of 2% for $0° \leq \psi \leq 360°$.[37] This value is about half the typical range of measured azimuthal angle dependence for the 20 Sources at 2 cm, and approximately equal to the measured result at 4 cm. While the origin of the ^{103}Pd azimuthal anisotropy is due to physical effects of shielding by internal components, azimuthal anisotropy for the model S700 Source is due to asymmetric photon production within the tube.

F. In-water dosimetry parameters

Based on the larger radial range and improved spatial resolution of the Monte Carlo results, and the relatively small differences between Monte Carlo results and measured results, we recommend use of the Monte Carlo-derived datasets for $g_P(r)$ at all operating voltages. For the 2-D anisotropy function, the Monte Carlo-derived datasets are also recommended for $F(r,\theta)$ at all three operating voltages for similar reasons to the $g_P(r)$ choice, plus the improved angular resolution. While the dose rate at the reference position was determined, values of the dose rate constant are not provided since air kerma strength results were not available.

G. Uncertainty analysis

An uncertainty analysis is presented for the measurements and calculations performed in-water as recommended by the 2004 AAPM TG-43U1 report.

1. Measurement uncertainties

Double uncertainties (k=2) in the PTW model 34013 ionization chamber energy correction and exposure calibration coefficients were ± 1% and 2%, respectively. Precision of Source:detector positioning and anode motion within the sheath was ± 0.2 mm. Combined in quadrature, these uncertainties in positioning caused dosimetric uncertainties of 4.6% at r_0. No measurement-medium correction factor was ascribed since transverse-plane measurements of $g(r)$ with the ion chamber were directly performed in water. Variations in current and power supply voltage were much less than 1%. The quadrature sum of these Type B uncertainties is 4.6%. Taking the quadrature sum of this value with a Type A uncertainty of 3%, based on repetitive measurements of dose rate using the chamber for all Sources at all three operating voltages, gave a total k=2 uncertainty of 5.5% for measurement of $\dot{D}(r_0,\theta_0)$.

2. Calculation uncertainties

On average, the Monte Carlo statistical uncertainties (k=2) in calculations of dose to water at 1 cm and 5 cm on the transverse-plane ($\theta = 90°$) were 0.2% and 0.4%, respectively. The photoionization cross-sections used were those recommended in the 2004 AAPM TG-43U1 report, with k=2 uncertainties of 2.4% as reported by Rivard *et al.*[37] Averaged over the energy spectra for the three operating voltages, the impact of the photoionization cross-section uncertainty on the transverse-plane dose rate at 1 and 5 cm is 0.2% and 0.9%,

respectively. These are less than those reported by Rivard *et al.* for the ^{103}Pd source because of the higher-average photon energy of the Source. The estimated dosimetric impact of Source geometry uncertainties due to variation in anode thickness is 1.5%, and internal positioning (± 0.2 mm) within the sheath are 4% and 0.8% at 1 and 5 cm, respectively. Estimates of uncertainties in photon energy spectra on the transverse-plane, based on a Monte Carlo parametric study varying material thicknesses, indicate that the dosimetric impact of Source spectrum uncertainties could be as high as 2% and 8% at 1 and 5 cm, respectively. In total, the quadrature sum of these k=2 uncertainties on $\dot{d}(r = 1\,cm, \theta_0)$ and $\dot{d}(r = 5\,cm, \theta_0)$ are 4.7% and 8.2%, respectively. These uncertainties are comparable to those reported for other low-energy, photon-emitting sources.

IV. SUMMARY

This seminal report of the Xoft AXXENT™ X-Ray Source, an electronic brachytherapy source, presents the in-water brachytherapy dosimetry parameters, $\dot{D}(r_0, \theta_0)$, $g_P(r)$, and $F(r,\theta)$. These parameters were obtained using both measurements and calculations for three operating voltages. These data demonstrate customized depth-dose capabilities through varying the operating voltage. Furthermore, photon-energy spectra and azimuthal-angle dependence of in-water dose rate are presented. Additional research is in process at the University of Wisconsin to confirm results presented herein using different measurement techniques and Monte Carlo calculations. Finally, preparations are underway to perform a multi-institutional Phase I clinical trial for breast cancer using accelerated partial breast irradiation and a balloon-based catheter system.

ACKNOWLEDGEMENTS

Research support for some of the authors (M.J.R., S.D.D., and L.A.D.) was provided by Xoft, Inc. Tim Bohm of UW reviewed the AXXENT™ Monte Carlo Source model, Robert R. Burnside of Xoft, Inc. assisted with some of the experimental measurements, and Sou-Tung Chiu-Tsao provided enlightening discussions on the compatibility of these datasets with various treatment planning systems such as BrachyVision™ and PLATO™. Finally, Michael Mitch, Stephen Seltzer, and Michelle O'Brien of the National Institute of Standards and Technology are gratefully acknowledged for providing the preliminary HPGe photon-energy spectra measurements and for efforts towards establishing traceable reference-quality measurements.

[a] This work was presented in part at the 27th annual meeting of the American Brachytherapy Society on May 15, 2004, and at the 46th annual meeting of the American Association of Physicists in Medicine on July 28, 2004.

[b] Author to whom correspondence should be addressed; Electronic mail: mrivard@tufts-nemc.org

[1] T. W. Rusch and M. J. Rivard, "Application of the TG-43 dosimetry protocol to electronic brachytherapy sources," Radiotherapy Oncol. **71(S2)**, S84 [abstract] (2004).

[2] S. Chiu-Tsao, T. Rusch, S. Axelrod, H. Tsao, and L. Harrison, "Dose response of GafChromic XR-T film to a new electronic brachytherapy source," Radiotherapy Oncol. **71(S2)**, S84 [abstract] (2004).

[3] T. Rusch, S. Davis, L. DeWerd, R. Burnside, S. Axelrod, and M. Rivard, "Characterization of a new miniature x-ray source for electronic brachytherapy," Med. Phys. **31**, 1807 [abstract] (2004).

[4] S. Chiu-Tsao, T. Rusch, S. Axelrod, H. Tsao, and L. Harrison, "Radiochromic film dosimetry for a new electronic brachytherapy source," Med. Phys. **31**, 1913 [abstract] (2004).

[5] J. Fowler, R. Dale, and T. Rusch, "Variation of RBE with dose and dose rate for a miniature electronic brachytherapy source," Med. Phys. **31**, 1927 [abstract] (2004).

[6] R. M. Douglas, J. Beatty, K. Gall, R. F. Valenzuela, P. Biggs, P. Okunieff, and F. S. Pardo, "Dosimetric results from a feasibility study of a novel radiosurgical source for irradiation of intracranial metastases," Int. J. Radiat. Oncol. Biol. Phys. **36**, 443-450 (1996).

[7] J. S. Vaidya, M. Baum, J. S. Tobias, D. D'Souza, S. V. Naidu, S. Morgan, M. Metaxas, K. J. Harte, A. P. Sliski, and E. Thomson, "*Tar*geted *i*ntraoperative Radio*t*herapy (*Targit*): An innovative method of treatment for early breast cancer," Ann. Oncol. **12**, 1075-1080 (2001).

[8] J. S. Vaidya, M. Baum, J. S. Tobias, S. Morgan, and D. D'Souza, "The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer," Eur. J. Surg. Oncol. **28**, 447-454 (2002).

[9] M. Dinsmore, K. J. Harte, A. P. Sliski, D. O. Smith, P. M. Nomikos, M. J. Dalterio, A. J. Boom, W. F. Leonard, P. E. Oettinger, and J. C. Yanch, "A new miniature x-ray source for interstitial radiosurgery: Device description," Med. Phys. **23**, 45-52 (1996).

[10] J. Beatty, P. J. Biggs, K. Gall, P. Okunieff, F. S. Pardo, K. J. Harte, M. J. Dalterio, and A. P. Sliski, "A new miniature x-ray source for interstitial radiosurgery: Dosimetry," Med. Phys. **23**, 53-62 (1996).

[11] J. C. Yanch and K. J. Harte, "Monte Carlo simulation of a miniature, radiosurgery x-ray tube using the ITS 3.0 coupled electron-photon transport code," Med. Phys. **23**, 1551-1558 (1996).

[12] R. Nath, L. L. Anderson, G. Luxton, K. A. Weaver, J. F. Williamson, and A. S. Meigooni, "Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43," Med. Phys. **22**, 209-234 (1995).

[13] M. J. Rivard, B. M. Coursey, L. A. DeWerd, W. F. Hanson, M. S. Huq, G. S. Ibbott, M. G. Mitch, R. Nath, and J. F. Williamson, "Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations (AAPM Report No. 84)," Med. Phys. **31**, 633-674 (2004).

[14] B. Fraass, K. Doppke, M. Hunt, G. Kutcher, G. Starkschall, R. Stern, and J. Van Dyke, "American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53: Quality assurance for clinical radiotherapy treatment planning," Med. Phys. **25**, 1773-1829 (1998).

[15] J. F. Williamson, B. M. Coursey, L. A. DeWerd, W. F. Hanson, and R. Nath, "Dosimetric prerequisites for routine clinical use of new low energy photon interstitial brachytherapy sources," Med. Phys. **25**, 2269-2270 (1998). http://rpc.mdanderson.org/rpc/htm/Home_htm/Low-energy.htm (last accessed August 20, 2006).

[16] J. W. Motz and R. C. Placious, "Bremsstrahlung cross-section measurements for 50 keV electrons," Phys. Rev. **109** 235-242 (1958).

[17] M. J. Berger and S. M. Seltzer, "Bremsstrahlung and photoneutrons from thick tungsten targets," Phys. Rev. C **2** 621-631 (1970).

[18] J. J. DeMarco, T. D. Solberg, R. E. Wallace, and J. B. Smathers, "A verification of the Monte Carlo code MCNP for thick target bremsstrahlung calculations," Med. Phys. **22** 11-16 (1995).

[19] J. R. Mercier, D. T. Kopp, W. D. McDavid, S. B. Dove, J. L. Lancaster, and D. M. Tucker, "Modification and benchmarking of MCNP for low-energy tungsten spectra," Med. Phys. **27** 2680-2687 (2000).

[20] S. Gallardo, J. Rodenas, and G. Verdu, "Monte Carlo simulation of the Compton scattering technique applied to characterize diagnostic x-ray spectra," Med. Phys. **31** 2082-2090 (2004).

[21] B. Wang, C-H. Kim, X. G. Xu, "Monte Carlo modeling of a high-sensitivity MOSFET dosimeter for low- and medium energy photon sources," Med. Phys. **31** 1003-1008 (2004).

[22] C. Austerlitz, H. P. Villar, M. A. P. Santos, "Influence of field size on a PTW type 23342 plane-parallel ionization chamber's response," Med. Phys. **31** 3201-3205 (2004).

[23] M. R. Ay, S. Sakar, M. Shahriari, D. Sardari, and H. Zaidi, "Assessment of different computational models for generation of x-ray spectra in diagnostic radiology and mammography," Med. Phys. **32** 1660-1675 (2005).

[24] J. M. Boone and J. A Siebert, "An accurate method for computer-generated tungsten anode x-ray spectra for 30 to 140 kV," Med. Phys. 24 1661-1670 (1997).

[25] X-5 Monte Carlo Team. MCNP – A general Monte Carlo N-Particle transport code, Version 5, Los Alamos National Laboratory, Los Alamos, NM (2003).

[26] Cross Section Evaluation Working Group. "ENDF/B-VI Summary Documentation (ENDF-201)," Brookhaven National Laboratory report BNL-NCS-17541, 8th Edition, National Nuclear Data Center (December 2000).

[27] D. E. Cullen, J. H. Hubbell, and L. Kissel, "EPDL97: The Evaluated Photon Data Library, '97 Version," Lawrence Livermore National Laboratory report UCRL-50400, Vol. 6, Revision 5 (September 19, 1997).

[28] C. W. Morgan, "Photoatomic Data Library MCPLIB04: A new photoatomic library based on data from ENDF/B-VI Release 8," Los Alamos National Laboratory report LA-UR-03-1019 L-50400, Vol. 6, Revision 5 (September 19, 1997).

[29] J. H. Hubbell, J. S. Coursey, J. Hwang, and D. S. Zucker. Bibliography of Photon Total Cross Section (Attenuation Coefficient) Measurements (online version 2.2): http://physics.nist.gov/photoncs (last accessed August 20, 2006) National Institute of Standards and Technology, Gaithersburg, MD (1998).

[30] S. M. Seltzer, "Calculation of photon mass energy-transfer and mass energy-absorption coefficients," Rad. Res. **136,** 147-170 (1993). See also http://physics.nist.gov/PhysRefData/XrayMassCoef/cover.html (last accessed August 20, 2006).

[31] J. J. DeMarco, R. E. Wallace, and K. Boedeker, "An analysis of MCNP cross-sections and tally methods for low-energy photon emitters," Phys. Med. Biol. **47**, 1321-1332 (2002).

[32] RSICC Data Library DLC-220, Radiation Safety Information Computational Center, Oak Ridge National Laboratory, http://www-rsicc.ornl.gov/codes/dlc/dlc2/dlc-220.html (last accessed August 20, 2006).

[33] D. M. Duggan, "Improved radial dose function estimation using current version MCNP Monte-Carlo simulation: Model 6711 and ISC3500 ^{125}I brachytherapy sources," Appl. Radiat. Isot. **61**, 1443-1450 (2004).

[34] J. Pérez-Calatayud, D. Granero, and F. Ballester, "Phantom size in brachytherapy source dosimetric studies," Med. Phys. **31**, 2075-2081 (2004).

[35] C. S. Melhus and M. J. Rivard, "Approaches to calculating AAPM TG-43 brachytherapy dosimetry parameters for ^{137}Cs, ^{125}I, ^{192}Ir, ^{103}Pd, and ^{169}Yb sources," Med. Phys. **33**, 1729-1737 (2006).

[36] G. M. Daskalov, E. Löffler, and J. F. Williamson, "Monte Carlo-aided dosimetry of a new high dose-rate brachytherapy source," Med. Phys. **25**, 2200-2208 (1998).

[37] M. J. Rivard, C. S. Melhus, and B. L. Kirk, "Brachytherapy dosimetry parameters calculated for a new ^{103}Pd source," Med. Phys. **31**, 2466-2470 (2004).

Table I. Measured and calculated dose rates to water at the reference position (r_0, θ_0) for the AXXENT™ Source at operating voltages of 40, 45, and 50 kV. Measurements were taken using a PTW 34013 ionization chamber in 11 × 29 × 29 cm^3 liquid water bath, and calculations used MCNP5 in a 20 cm radius spherical liquid water phantom. The average measured readings were used to derive the ratio in the last line.

	$P(r_0,\theta_0)$ water dose rate [cGy h^{-1} μA^{-1}]		
source	40 kV	45 kV	50 kV
measured maximum	241	304	357
measured average	129	196	265
calculated MCNP5	254	325	382
measured/calculated	0.54	0.64	0.74

480 **Table II.** Calculated and measured radial dose function values using the point-source model for the 40, 45, and 50 kV voltage settings for the model S700 AXXENT™ Source. Measured results were for n=3, n=3, and n=20 tubes for 40, 45, and 50 kV, respectively. Calculated and measured results were obtained with 1 mm and 2mm precision, respectively. While ratios of measured-to-calculated $g_P(r)^{50}$ approach 1.15 for large r, all differences are smaller than the measured uncertainties. Log-linear interpolation of measured results are presented in
485 boldface, and result in errors < 1 % which are much less than the uncertainties.

	calculated			measured			measured – calculated		
r [cm]	$_{MC}g_P(r)^{40}$	$_{MC}g_P(r)^{45}$	$_{MC}g_P(r)^{50}$	$_{PTW}g_P(r)^{40}$	$_{PTW}g_P(r)^{45}$	$_{PTW}g_P(r)^{50}$	$g_P(r)^{40}$	$g_P(r)^{45}$	$g_P(r)^{50}$
0.4	1.678	1.603	1.551						
0.5	1.511	1.455	1.418						
0.6	1.373	1.332	1.305						
0.7	1.257	1.230	1.211						
0.8	1.159	1.142	1.131						
0.9	1.074	1.066	1.061						
1.0	1.000	1.000	1.000	1.000	1.000	1.000	0.000	0.000	0.000
1.1	0.935	0.941	0.946	**0.942**	**0.948**	**0.960**	0.007	0.007	0.014
1.2	0.877	0.889	0.898	0.887	0.899	0.920	0.010	0.010	0.022
1.3	0.825	0.842	0.855	**0.838**	**0.853**	**0.884**	0.013	0.011	0.029
1.4	0.778	0.799	0.816	0.792	0.809	0.848	0.014	0.010	0.032
1.5	0.736	0.761	0.780	**0.751**	**0.771**	**0.817**	0.015	0.010	0.037
1.6	0.698	0.726	0.748	0.711	0.735	0.786	0.013	0.009	0.038
1.7	0.662	0.694	0.718	**0.677**	**0.703**	**0.759**	0.015	0.009	0.041
1.8	0.630	0.664	0.690	0.644	0.673	0.732	0.014	0.009	0.042
1.9	0.600	0.637	0.665	**0.614**	**0.645**	**0.707**	0.014	0.008	0.042
2.0	0.573	0.612	0.641	0.585	0.619	0.683	0.012	0.007	0.042
2.5	0.462	0.507	0.544	**0.473**	**0.513**	**0.588**	0.011	0.006	0.044
3.0	0.381	0.430	0.470	0.389	0.434	0.511	0.008	0.004	0.041
3.5	0.318	0.369	0.411	**0.326**	**0.372**	**0.450**	0.008	0.003	0.039
4.0	0.269	0.320	0.362	0.275	0.323	0.399	0.006	0.003	0.037
4.5	0.229	0.278	0.322	**0.234**	**0.281**	**0.355**	0.005	0.003	0.033
5.0	0.196	0.244	0.286	0.200	0.246	0.317	0.004	0.002	0.031
5.5	0.168	0.214	0.256	**0.174**	**0.216**	**0.284**	0.006	0.002	0.028
6.0	0.145	0.189	0.229	0.150	0.192	0.256	0.005	0.003	0.027
6.5	0.126	0.167	0.206	**0.131**	**0.170**	**0.232**	0.005	0.003	0.026
7.0	0.109	0.148	0.185	0.112	0.151	0.213	0.003	0.003	0.028
7.5	0.0943	0.131	0.166						
8.0	0.0818	0.116	0.150						
8.5	0.0712	0.103	0.135						
9.0	0.0620	0.0917	0.122						
9.5	0.0542	0.0812	0.110						
10.0	0.0472	0.0723	0.0989						
10.5	0.0413	0.0643	0.0890						
11.0	0.0361	0.0574	0.0804						
11.5	0.0315	0.0510	0.0725						
12.0	0.0276	0.0455	0.0655						
12.5	0.0241	0.0405	0.0591						
13.0	0.0211	0.0361	0.0534						
13.5	0.0185	0.0321	0.0481						
14.0	0.0162	0.0287	0.0434						
14.5	0.0141	0.0255	0.0392						
15.0	0.0124	0.0227	0.0352						

Table III. Calculated 2-D anisotropy function data, $F(r,\theta)^{40}$, for the AXXENT™ Source at 40 kV.

θ [degrees]	radial distance, r [cm]												
	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	15.0
0°	0.903	0.945	0.977	0.994	1.023	1.033	1.049	1.054	1.061	1.070	1.082	1.086	1.098
5°	0.898	0.945	0.972	0.993	1.018	1.036	1.050	1.059	1.062	1.069	1.079	1.085	1.102
10°	0.889	0.942	0.973	0.997	1.023	1.039	1.051	1.063	1.065	1.071	1.086	1.092	1.100
15°	0.892	0.946	0.976	0.996	1.022	1.039	1.050	1.064	1.072	1.072	1.084	1.093	1.105
20°	0.898	0.949	0.979	0.999	1.023	1.040	1.052	1.061	1.066	1.074	1.084	1.089	1.094
25°	0.894	0.947	0.977	0.996	1.022	1.039	1.048	1.058	1.066	1.073	1.080	1.085	1.102
30°	0.922	0.953	0.975	0.991	1.013	1.031	1.046	1.054	1.061	1.069	1.080	1.087	1.100
35°	0.971	1.000	1.019	1.030	1.049	1.060	1.068	1.075	1.081	1.089	1.096	1.103	1.116
40°	1.012	1.037	1.052	1.061	1.072	1.080	1.085	1.089	1.096	1.102	1.108	1.118	1.129
45°	1.051	1.064	1.073	1.079	1.088	1.095	1.097	1.103	1.105	1.110	1.119	1.118	1.128
50°	1.073	1.081	1.087	1.091	1.096	1.100	1.102	1.105	1.107	1.112	1.118	1.123	1.128
55°	1.085	1.091	1.094	1.096	1.101	1.103	1.102	1.103	1.105	1.109	1.112	1.117	1.123
60°	1.091	1.095	1.097	1.097	1.097	1.098	1.099	1.101	1.102	1.105	1.108	1.113	1.112
65°	1.090	1.091	1.091	1.092	1.091	1.092	1.090	1.093	1.091	1.093	1.098	1.099	1.099
70°	1.084	1.084	1.082	1.081	1.080	1.079	1.079	1.079	1.079	1.081	1.084	1.084	1.089
75°	1.072	1.069	1.068	1.067	1.065	1.065	1.065	1.064	1.066	1.066	1.065	1.067	1.072
80°	1.052	1.050	1.048	1.047	1.046	1.045	1.044	1.044	1.042	1.047	1.047	1.047	1.050
85°	1.028	1.028	1.027	1.026	1.027	1.026	1.024	1.024	1.021	1.023	1.021	1.025	1.024
90°	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
95°	0.965	0.970	0.972	0.973	0.974	0.975	0.974	0.974	0.973	0.977	0.976	0.969	0.969
100°	0.932	0.937	0.940	0.942	0.945	0.945	0.946	0.945	0.945	0.947	0.943	0.943	0.943
105°	0.896	0.900	0.905	0.909	0.914	0.916	0.916	0.917	0.915	0.916	0.916	0.915	0.916
110°	0.853	0.858	0.866	0.871	0.879	0.881	0.883	0.884	0.882	0.881	0.883	0.880	0.869
115°	0.807	0.812	0.822	0.830	0.838	0.844	0.846	0.846	0.846	0.850	0.846	0.847	0.841
120°	0.756	0.759	0.770	0.780	0.790	0.798	0.801	0.802	0.804	0.805	0.801	0.801	0.797
125°	0.695	0.691	0.702	0.713	0.730	0.743	0.749	0.753	0.756	0.757	0.759	0.756	0.757
130°	0.615	0.604	0.622	0.639	0.663	0.680	0.690	0.698	0.701	0.706	0.709	0.706	0.701
135°	0.495	0.508	0.536	0.560	0.593	0.615	0.627	0.638	0.642	0.650	0.653	0.655	0.656
140°	0.363	0.411	0.449	0.478	0.519	0.547	0.564	0.576	0.584	0.592	0.598	0.603	0.600
145°	0.211	0.318	0.362	0.396	0.444	0.475	0.496	0.514	0.524	0.534	0.543	0.550	0.550
150°	NA	0.248	0.298	0.333	0.384	0.418	0.440	0.455	0.469	0.480	0.489	0.498	0.503
155°	NA	0.164	0.213	0.254	0.309	0.349	0.376	0.394	0.409	0.419	0.436	0.447	0.452
160°	NA	0.168	0.205	0.237	0.286	0.317	0.343	0.360	0.373	0.383	0.400	0.405	0.410
165°	NA	0.194	0.217	0.242	0.281	0.309	0.329	0.344	0.356	0.367	0.376	0.381	0.381
170°	NA	NA	0.199	0.218	0.258	0.285	0.309	0.324	0.339	0.342	0.356	0.368	0.372
175°	NA	NA	NA	NA	0.211	0.243	0.268	0.292	0.304	0.317	0.330	0.349	0.352

NA indicates the position is located within the model S700 AXXENT™ Source and the dosimetry formalism is not applicable.

Table IV. Calculated 2-D anisotropy function data, $F(r,\theta)^{45}$, for the AXXENT™ Source at 45 kV.

θ	radial distance, r [cm]												
[degrees]	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	15.0
0°	0.910	0.961	0.998	1.015	1.039	1.047	1.065	1.069	1.064	1.085	1.096	1.111	1.114
5°	0.908	0.956	0.985	1.005	1.030	1.050	1.063	1.071	1.080	1.086	1.097	1.112	1.103
10°	0.899	0.955	0.989	1.009	1.037	1.051	1.066	1.077	1.078	1.088	1.096	1.109	1.119
15°	0.901	0.956	0.989	1.011	1.036	1.055	1.068	1.076	1.081	1.088	1.099	1.104	1.116
20°	0.905	0.962	0.994	1.013	1.037	1.052	1.065	1.074	1.084	1.089	1.099	1.106	1.112
25°	0.905	0.962	0.993	1.011	1.038	1.053	1.066	1.073	1.079	1.090	1.100	1.103	1.116
30°	0.930	0.963	0.987	1.004	1.028	1.044	1.057	1.066	1.073	1.083	1.097	1.103	1.112
35°	0.975	1.007	1.028	1.039	1.057	1.069	1.078	1.085	1.088	1.095	1.106	1.119	1.120
40°	1.014	1.041	1.058	1.065	1.078	1.087	1.092	1.096	1.100	1.104	1.114	1.119	1.127
45°	1.051	1.066	1.077	1.082	1.091	1.095	1.100	1.102	1.106	1.110	1.117	1.122	1.128
50°	1.073	1.082	1.090	1.093	1.099	1.101	1.105	1.106	1.107	1.110	1.117	1.120	1.127
55°	1.084	1.090	1.095	1.096	1.099	1.101	1.103	1.104	1.104	1.108	1.112	1.113	1.115
60°	1.087	1.092	1.095	1.095	1.095	1.096	1.097	1.097	1.098	1.102	1.105	1.107	1.105
65°	1.088	1.089	1.090	1.088	1.088	1.087	1.088	1.087	1.088	1.089	1.092	1.096	1.099
70°	1.080	1.080	1.080	1.078	1.078	1.077	1.076	1.075	1.075	1.078	1.080	1.082	1.081
75°	1.069	1.066	1.066	1.064	1.061	1.061	1.060	1.060	1.058	1.061	1.062	1.062	1.060
80°	1.050	1.049	1.048	1.045	1.044	1.042	1.041	1.042	1.042	1.043	1.043	1.044	1.045
85°	1.028	1.026	1.026	1.024	1.023	1.023	1.023	1.021	1.022	1.022	1.025	1.024	1.022
90°	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
95°	0.968	0.970	0.973	0.974	0.974	0.976	0.977	0.975	0.976	0.976	0.976	0.974	0.970
100°	0.937	0.940	0.944	0.945	0.948	0.950	0.950	0.949	0.949	0.949	0.951	0.947	0.947
105°	0.902	0.905	0.910	0.913	0.917	0.921	0.921	0.921	0.920	0.921	0.921	0.924	0.918
110°	0.863	0.866	0.874	0.878	0.884	0.889	0.890	0.892	0.892	0.892	0.892	0.889	0.889
115°	0.818	0.821	0.830	0.837	0.847	0.852	0.857	0.858	0.858	0.859	0.860	0.857	0.854
120°	0.767	0.769	0.782	0.791	0.802	0.810	0.815	0.818	0.820	0.822	0.822	0.820	0.818
125°	0.707	0.702	0.715	0.726	0.745	0.756	0.765	0.771	0.774	0.776	0.782	0.779	0.777
130°	0.627	0.618	0.638	0.654	0.681	0.698	0.710	0.718	0.722	0.729	0.730	0.733	0.732
135°	0.507	0.522	0.553	0.578	0.613	0.637	0.651	0.662	0.670	0.678	0.684	0.686	0.685
140°	0.375	0.425	0.466	0.498	0.541	0.571	0.590	0.605	0.613	0.620	0.633	0.636	0.637
145°	0.220	0.331	0.380	0.416	0.468	0.501	0.526	0.543	0.554	0.564	0.579	0.584	0.592
150°	NA	0.261	0.314	0.352	0.406	0.442	0.468	0.488	0.502	0.512	0.529	0.537	0.545
155°	NA	0.177	0.231	0.273	0.335	0.376	0.408	0.430	0.444	0.459	0.478	0.490	0.502
160°	NA	0.179	0.220	0.254	0.307	0.345	0.372	0.393	0.408	0.422	0.440	0.452	0.462
165°	NA	0.206	0.230	0.256	0.300	0.333	0.358	0.377	0.391	0.403	0.420	0.427	0.436
170°	NA	NA	0.213	0.232	0.277	0.310	0.337	0.356	0.369	0.385	0.401	0.411	0.417
175°	NA	NA	NA	NA	0.234	0.267	0.298	0.322	0.338	0.351	0.372	0.386	0.397

490 NA indicates the position is located within the model S700 AXXENT™ Source and the dosimetry formalism is not applicable.

Table V. Calculated 2-D anisotropy function data, $F(r,\theta)^{50}$, for the AXXENT™ Source at 50 kV.

θ	radial distance, r [cm]												
[degrees]	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	15.0
0°	0.908	0.962	0.991	1.016	1.038	1.059	1.072	1.081	1.091	1.092	1.102	1.107	1.122
5°	0.905	0.961	0.989	1.012	1.042	1.058	1.071	1.078	1.085	1.093	1.105	1.114	1.117
10°	0.902	0.960	0.993	1.014	1.042	1.062	1.072	1.083	1.090	1.095	1.103	1.113	1.123
15°	0.903	0.964	0.997	1.018	1.043	1.061	1.073	1.082	1.089	1.093	1.102	1.110	1.120
20°	0.910	0.969	1.001	1.022	1.047	1.063	1.074	1.082	1.088	1.095	1.102	1.111	1.119
25°	0.908	0.968	0.999	1.020	1.044	1.061	1.073	1.080	1.089	1.093	1.101	1.110	1.119
30°	0.933	0.969	0.994	1.012	1.035	1.051	1.064	1.073	1.083	1.086	1.098	1.105	1.113
35°	0.974	1.011	1.031	1.044	1.061	1.072	1.081	1.088	1.092	1.099	1.106	1.114	1.122
40°	1.012	1.043	1.058	1.068	1.078	1.087	1.091	1.098	1.101	1.105	1.111	1.115	1.123
45°	1.048	1.065	1.076	1.083	1.090	1.095	1.098	1.102	1.105	1.107	1.111	1.116	1.124
50°	1.067	1.081	1.087	1.091	1.095	1.098	1.102	1.103	1.106	1.107	1.111	1.114	1.121
55°	1.077	1.087	1.092	1.094	1.096	1.097	1.098	1.100	1.100	1.104	1.105	1.108	1.115
60°	1.081	1.089	1.091	1.092	1.091	1.092	1.093	1.094	1.094	1.095	1.096	1.102	1.106
65°	1.081	1.085	1.085	1.085	1.084	1.083	1.083	1.085	1.085	1.085	1.087	1.086	1.092
70°	1.074	1.076	1.075	1.074	1.072	1.072	1.072	1.072	1.072	1.072	1.072	1.074	1.077
75°	1.063	1.063	1.062	1.060	1.058	1.057	1.058	1.057	1.057	1.057	1.056	1.057	1.058
80°	1.047	1.046	1.044	1.043	1.041	1.041	1.041	1.041	1.040	1.040	1.041	1.041	1.041
85°	1.025	1.024	1.024	1.022	1.020	1.021	1.021	1.020	1.021	1.022	1.021	1.020	1.022
90°	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
95°	0.970	0.973	0.975	0.976	0.977	0.977	0.977	0.979	0.978	0.978	0.977	0.976	0.976
100°	0.941	0.944	0.946	0.949	0.950	0.953	0.954	0.955	0.954	0.953	0.952	0.952	0.951
105°	0.908	0.910	0.914	0.918	0.923	0.925	0.928	0.929	0.929	0.927	0.927	0.926	0.925
110°	0.871	0.872	0.878	0.883	0.890	0.895	0.897	0.898	0.899	0.899	0.899	0.898	0.896
115°	0.828	0.828	0.837	0.845	0.855	0.860	0.865	0.869	0.869	0.868	0.869	0.869	0.868
120°	0.777	0.780	0.791	0.800	0.812	0.820	0.825	0.830	0.833	0.834	0.835	0.834	0.834
125°	0.718	0.713	0.725	0.739	0.758	0.771	0.781	0.787	0.792	0.795	0.798	0.799	0.799
130°	0.638	0.629	0.650	0.669	0.697	0.716	0.729	0.739	0.744	0.748	0.754	0.758	0.759
135°	0.519	0.537	0.568	0.594	0.630	0.656	0.673	0.685	0.693	0.699	0.708	0.713	0.716
140°	0.388	0.441	0.484	0.515	0.561	0.592	0.614	0.630	0.640	0.648	0.662	0.668	0.672
145°	0.230	0.347	0.397	0.435	0.488	0.525	0.550	0.572	0.585	0.595	0.610	0.619	0.628
150°	NA	0.275	0.330	0.370	0.428	0.467	0.495	0.518	0.533	0.545	0.562	0.573	0.582
155°	NA	0.193	0.250	0.294	0.359	0.404	0.437	0.462	0.481	0.495	0.515	0.530	0.540
160°	NA	0.193	0.236	0.272	0.329	0.370	0.401	0.425	0.443	0.458	0.479	0.495	0.507
165°	NA	0.220	0.244	0.271	0.320	0.356	0.384	0.407	0.423	0.438	0.455	0.470	0.483
170°	NA	NA	0.226	0.248	0.297	0.334	0.362	0.385	0.403	0.416	0.436	0.449	0.461
175°	NA	NA	NA	NA	0.251	0.290	0.320	0.346	0.369	0.386	0.410	0.424	0.443

NA indicates the position is located within the model S700 AXXENT™ Source and the dosimetry formalism is not applicable.

495 **Table VI.** Measured F(r,θ) and comparisons to calculated results for the model S700 AXXENT™ Source.

θ [degrees]	measured			measured/calculated		
	$F(2,\theta)^{40}$	$F(2,\theta)^{45}$	$F(2,\theta)^{50}$	${}^{PTW}_{MCNP}F(2,\theta)^{40}$	${}^{PTW}_{MCNP}F(2,\theta)^{45}$	${}^{PTW}_{MCNP}F(2,\theta)^{50}$
°	0.976	0.997	0.993	0.98	0.98	0.98
10°	0.986	1.008	1.001	0.99	1.00	0.99
20°	1.000	1.022	1.013	1.00	1.01	0.99
30°	1.011	1.031	1.024	1.01	1.02	1.00
40°	1.052	1.066	1.052	1.00	1.00	0.99
50°	1.077	1.087	1.072	0.99	1.00	0.98
60°	1.082	1.087	1.075	0.99	0.99	0.98
70°	1.069	1.072	1.063	0.99	1.00	0.99
80°	1.042	1.044	1.037	0.99	1.00	0.99
100°	0.943	0.946	0.953	1.00	1.00	1.00
110°	0.874	0.879	0.895	1.00	1.00	1.01
120°	0.789	0.798	0.820	1.02	1.01	1.03
130°	0.667	0.679	0.709	1.05	1.04	1.06
140°	0.512	0.530	0.564	1.07	1.07	1.09
		solid-angle weighted average ratio		1.01	1.01	1.01
θ [degrees]	$F(3,\theta)^{40}$	$F(3,\theta)^{45}$	$F(3,\theta)^{50}$	${}^{PTW}_{MCNP}F(3,\theta)^{40}$	${}^{PTW}_{MCNP}F(3,\theta)^{45}$	${}^{PTW}_{MCNP}F(3,\theta)^{50}$
°	0.997	1.021	1.018	0.98	0.98	0.98
10°	1.012	1.036	1.027	0.99	1.00	0.99
20°	1.025	1.048	1.037	1.00	1.01	0.99
30°	1.033	1.053	1.042	1.01	1.02	1.00
40°	1.068	1.083	1.065	1.00	1.01	0.99
50°	1.085	1.095	1.080	0.99	1.00	0.99
60°	1.085	1.092	1.079	0.99	1.00	0.99
70°	1.071	1.074	1.065	0.99	1.00	0.99
80°	1.042	1.044	1.038	1.00	1.00	1.00
100°	0.945	0.947	0.954	1.00	1.00	1.00
110°	0.877	0.882	0.896	1.00	1.00	1.01
120°	0.796	0.803	0.824	1.01	1.00	1.02
130°	0.681	0.695	0.721	1.03	1.02	1.04
140°	0.539	0.558	0.590	1.04	1.03	1.05
150°	0.383	0.402	0.426	1.01	0.99	1.00
		solid-angle weighted average ratio		1.00	1.00	1.00
θ [degrees]	$F(5,\theta)^{40}$	$F(5,\theta)^{45}$	$F(5,\theta)^{50}$	${}^{PTW}_{MCNP}F(5,\theta)^{40}$	${}^{PTW}_{MCNP}F(5,\theta)^{45}$	${}^{PTW}_{MCNP}F(5,\theta)^{50}$
°	1.024	1.050	1.050	0.99	0.99	0.97
10°	1.029	1.056	1.054	0.98	0.99	0.98
20°	1.041	1.066	1.059	0.99	1.00	0.99
30°	1.054	1.075	1.065	1.01	1.01	1.00
40°	1.072	1.087	1.075	0.99	1.00	0.98
50°	1.082	1.093	1.080	0.98	0.99	0.98
60°	1.080	1.087	1.075	0.98	0.99	0.98
70°	1.067	1.070	1.062	0.99	0.99	0.99
80°	1.043	1.041	1.036	1.00	1.00	1.00
100°	0.942	0.941	0.950	1.00	0.99	1.00
110°	0.875	0.891	0.894	0.99	1.00	1.00
120°	0.812	0.810	0.825	1.01	0.99	1.00
130°	0.705	0.711	0.731	1.02	1.00	1.00
140°	0.564	0.585	0.616	1.00	0.99	1.00
150°	0.413	0.443	0.473	0.94	0.95	0.96
160°	0.313	0.336	0.364	0.91	0.90	0.91
		solid-angle weighted average ratio		0.99	0.99	0.99
θ [degrees]	$F(7,\theta)^{40}$	$F(7,\theta)^{45}$	$F(7,\theta)^{50}$	${}^{PTW}_{MCNP}F(7,\theta)^{40}$	${}^{PTW}_{MCNP}F(7,\theta)^{45}$	${}^{PTW}_{MCNP}F(7,\theta)^{50}$
°	1.052	1.065	1.073	0.99	0.99	0.99
15°	1.057	1.071	1.076	0.99	0.99	0.99
25°	1.066	1.077	1.080	1.00	1.00	0.99
35°	1.075	1.087	1.083	0.99	1.00	0.99
45°	1.085	1.093	1.086	0.98	0.99	0.98
55°	1.085	1.093	1.086	0.98	0.99	0.99
65°	1.081	1.084	1.076	0.99	1.00	0.99
75°	1.062	1.063	1.056	1.00	1.01	1.00
85°	1.024	1.023	1.021	1.00	1.00	1.00
95°	0.976	0.977	0.979	1.00	1.00	1.00
105°	0.914	0.920	0.929	1.00	1.00	1.00
115°	0.840	0.849	0.866	0.99	0.99	1.00
125°	0.746	0.758	0.794	0.99	0.98	1.00
135°	0.631	0.650	0.692	0.98	0.97	1.00
145°	0.510	0.529	0.579	0.97	0.95	0.99
155°	0.404	0.428	0.429	0.99	0.96	0.89
165°	0.335	0.354	0.383	0.94	0.91	0.91
		solid-angle weighted average ratio		0.99	0.99	0.99

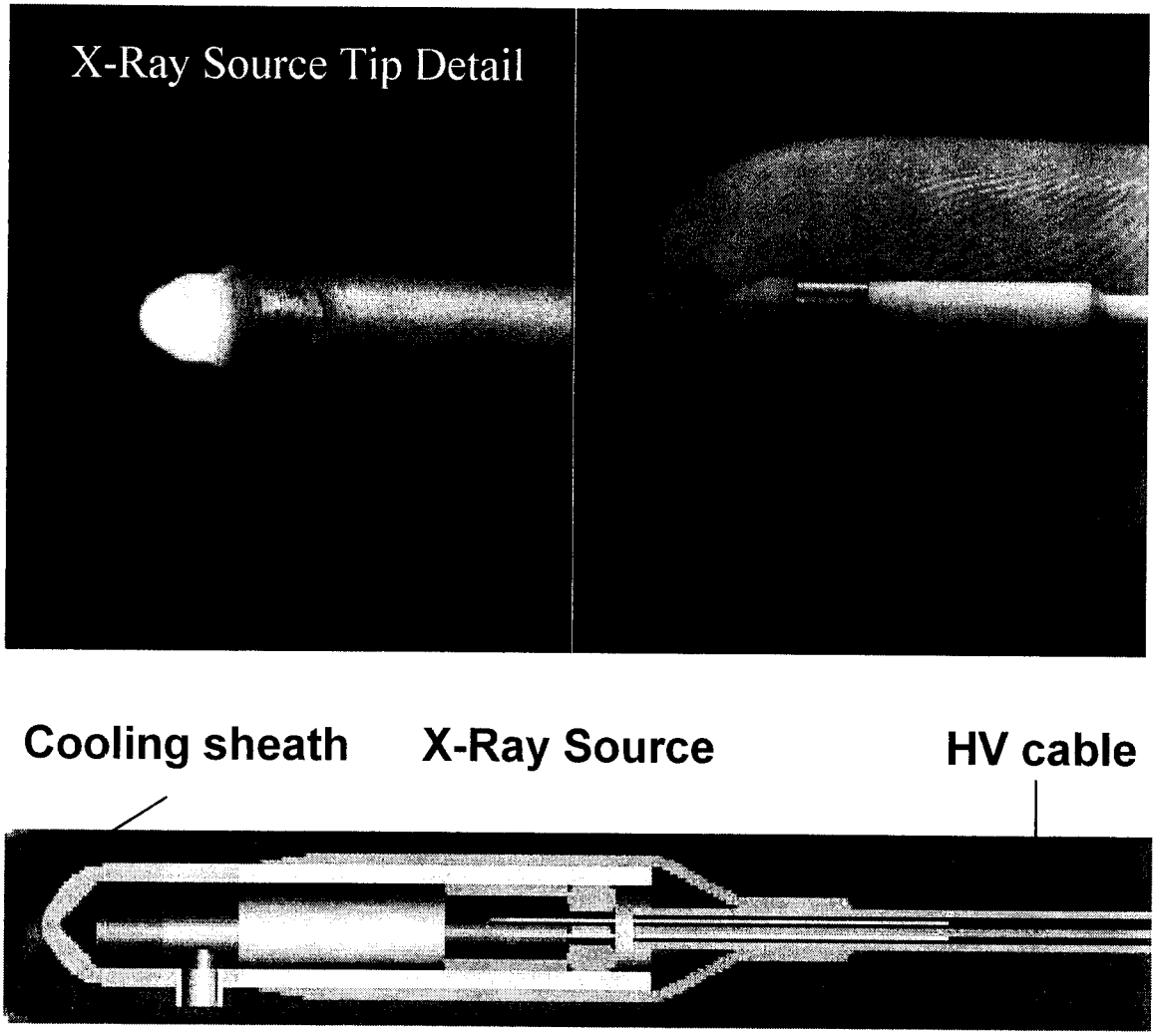


Fig. 1. Photographs and schematic diagram of the model S700 Xoft AXXENT™ X-Ray Source. The LHS image shows the model S700 Source in operation. The bottom illustration shows the Source enclosed by a gray water cooling sheath. The sheath outer diameter is 5.3 mm, and is flexible beyond the distal 15 mm.

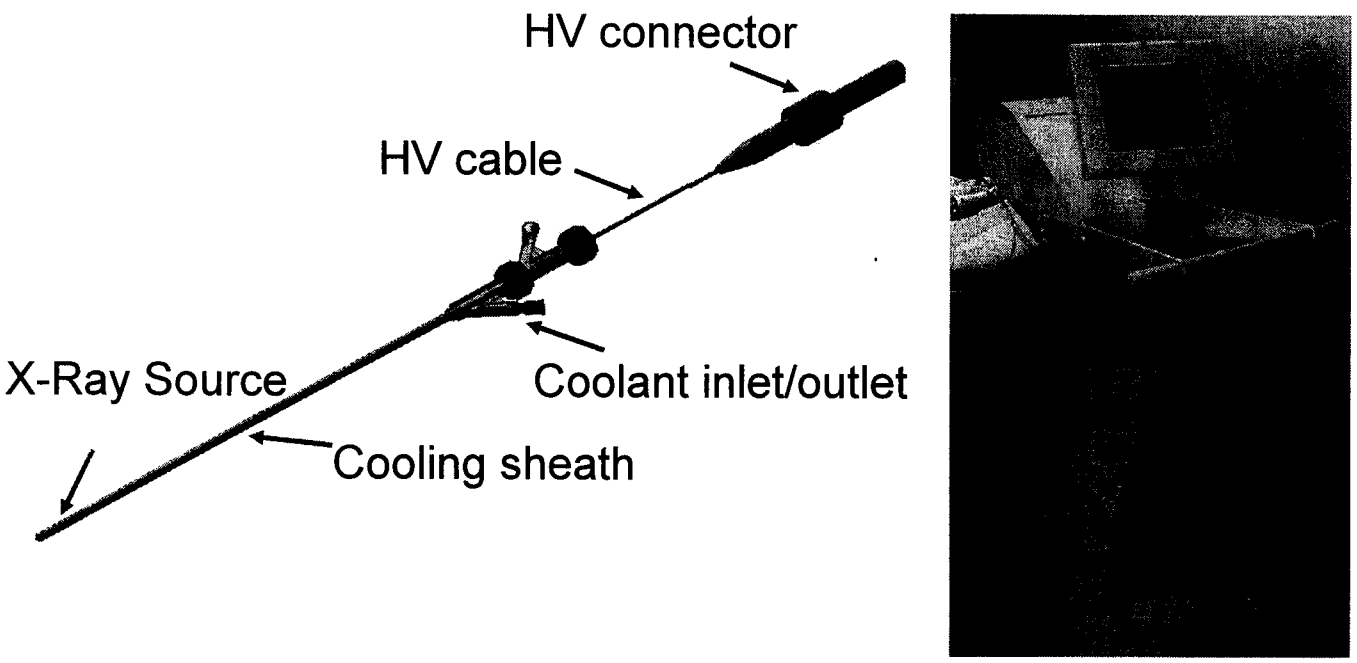


Fig. 2. Schematic diagram of the entire model S700 Source probe illustrating the relationship of the Source to the water coolant inlet/outlet and HV connector. Though depicted as a straight, needle-like device, in reality the probe is flexible. The RHS image shows the treatment control console adjacent to a radiotherapy stretcher bed.

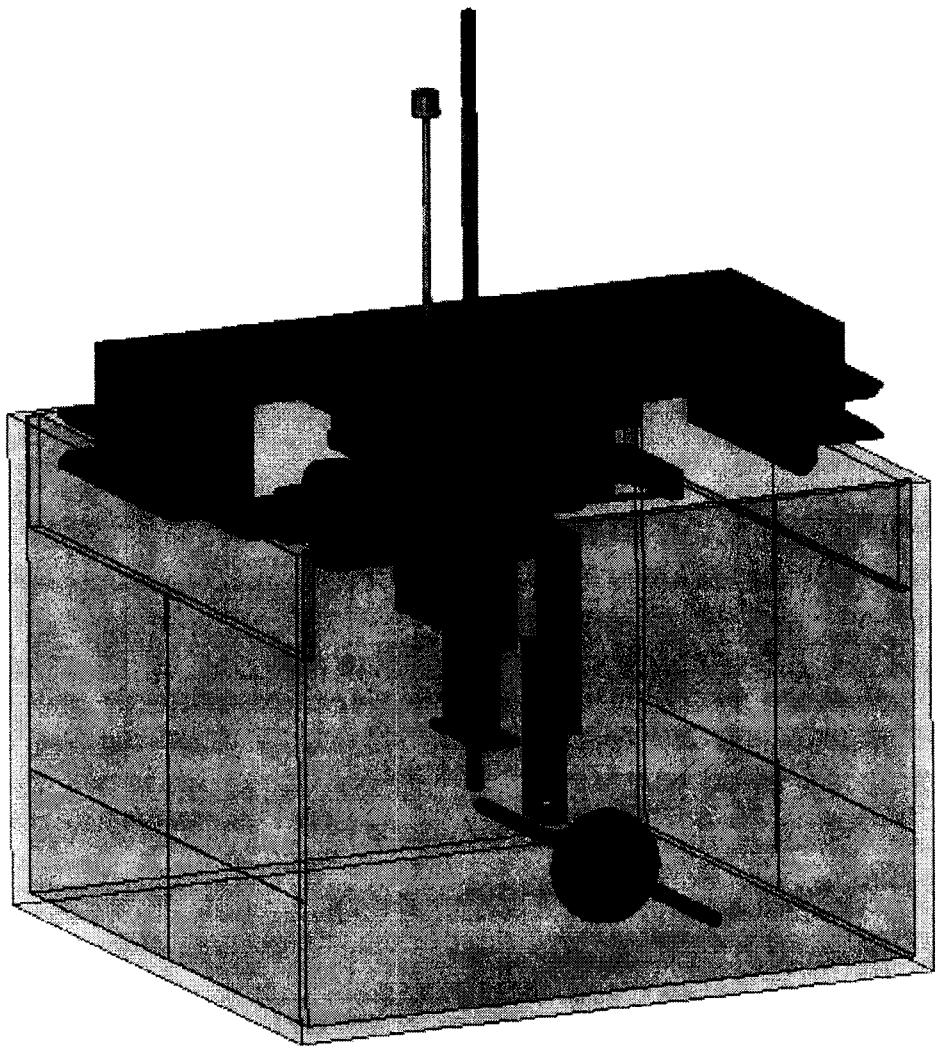


Fig. 3. Spatial measurement apparatus in water tank, surrounding radiation shielding not shown The structure at the top contains both rotary and linear stepper motors. Source catheters can enter from above for azimuthal, or through the front, for polar angle anisotropy function measurements. Radial dose function measurements can be made in either orientation. The ion chamber is encased in a sealed SolidWater™ box with a snorkel to allow equilibration with atmospheric pressure.

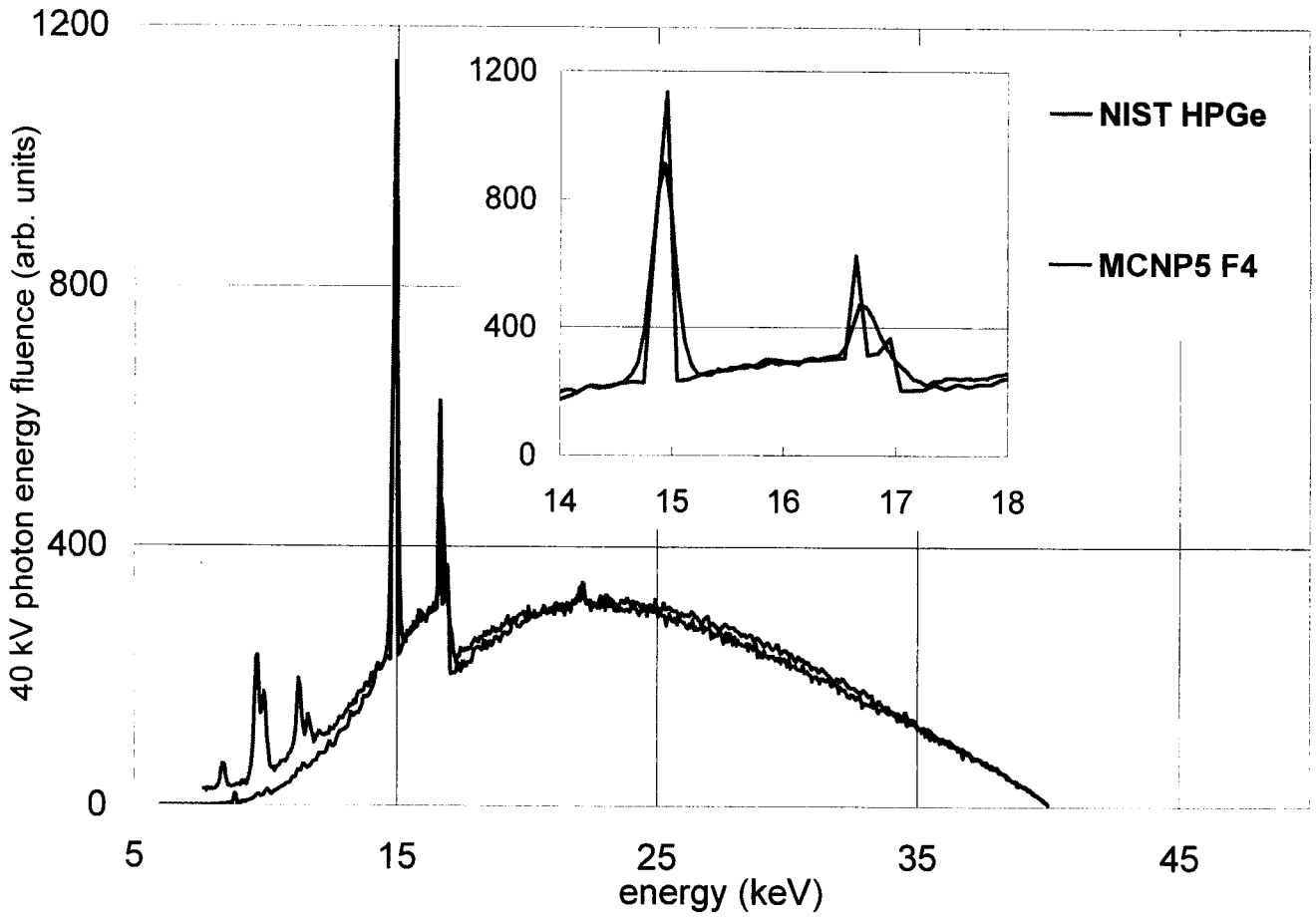


Fig. 4. Relative photon energy spectra at 40, 45, and 50 kV for the model S700 Source along the transverse-plane. Calculations were performed using MCNP version 5 with 100 eV bin widths. Measurements were obtained at NIST using a high-purity germanium (HPGe) detector and 60 eV bin widths for the multi-channel analyzer.

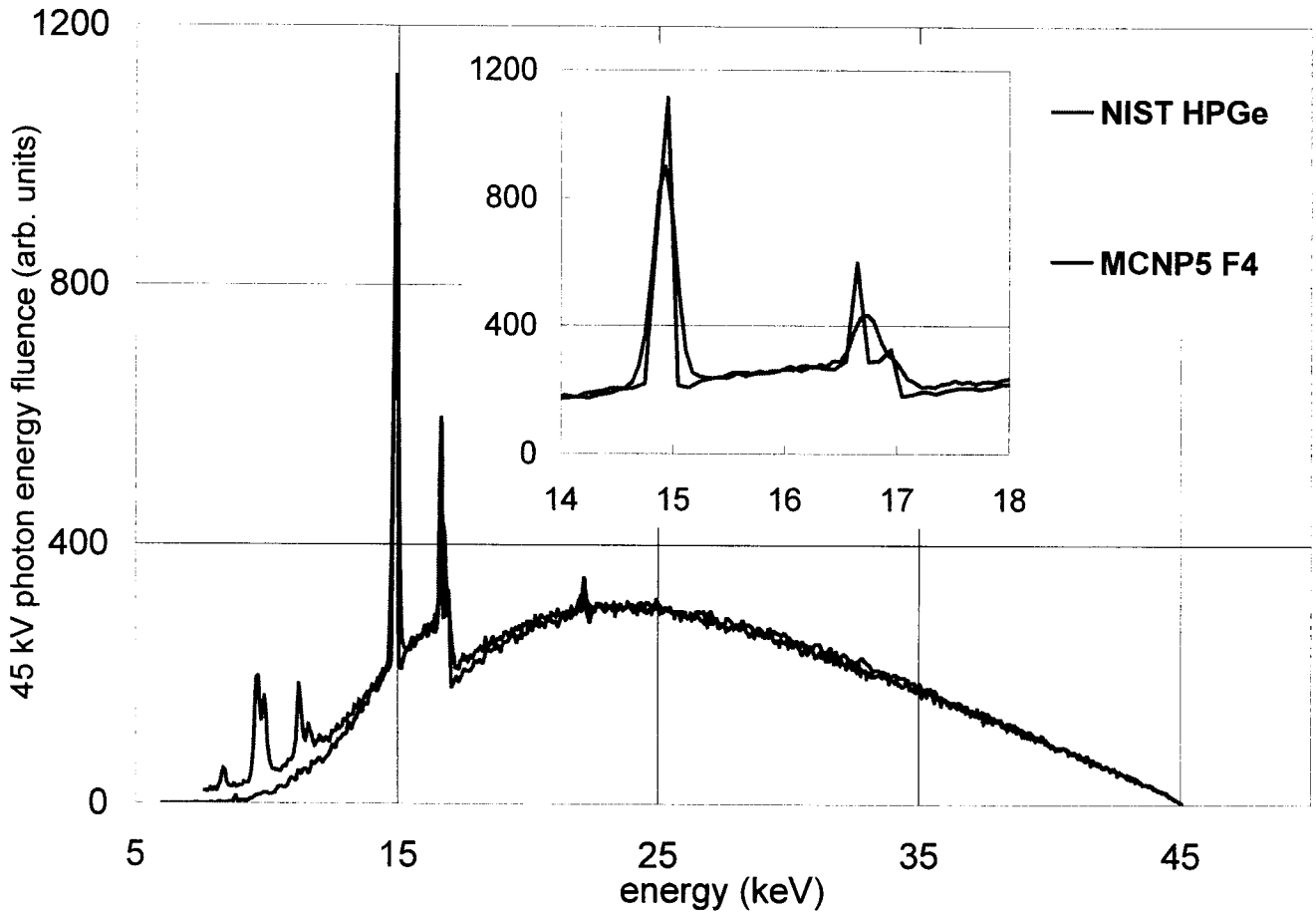


Fig. 4. Relative photon energy spectra at 40, 45, and 50 kV for the model S700 Source along the transverse-plane. Calculations were performed using MCNP version 5 with 100 eV bin widths. Measurements were obtained at NIST using a high-purity germanium (HPGe) detector and 60 eV bin widths for the multi-channel analyzer.

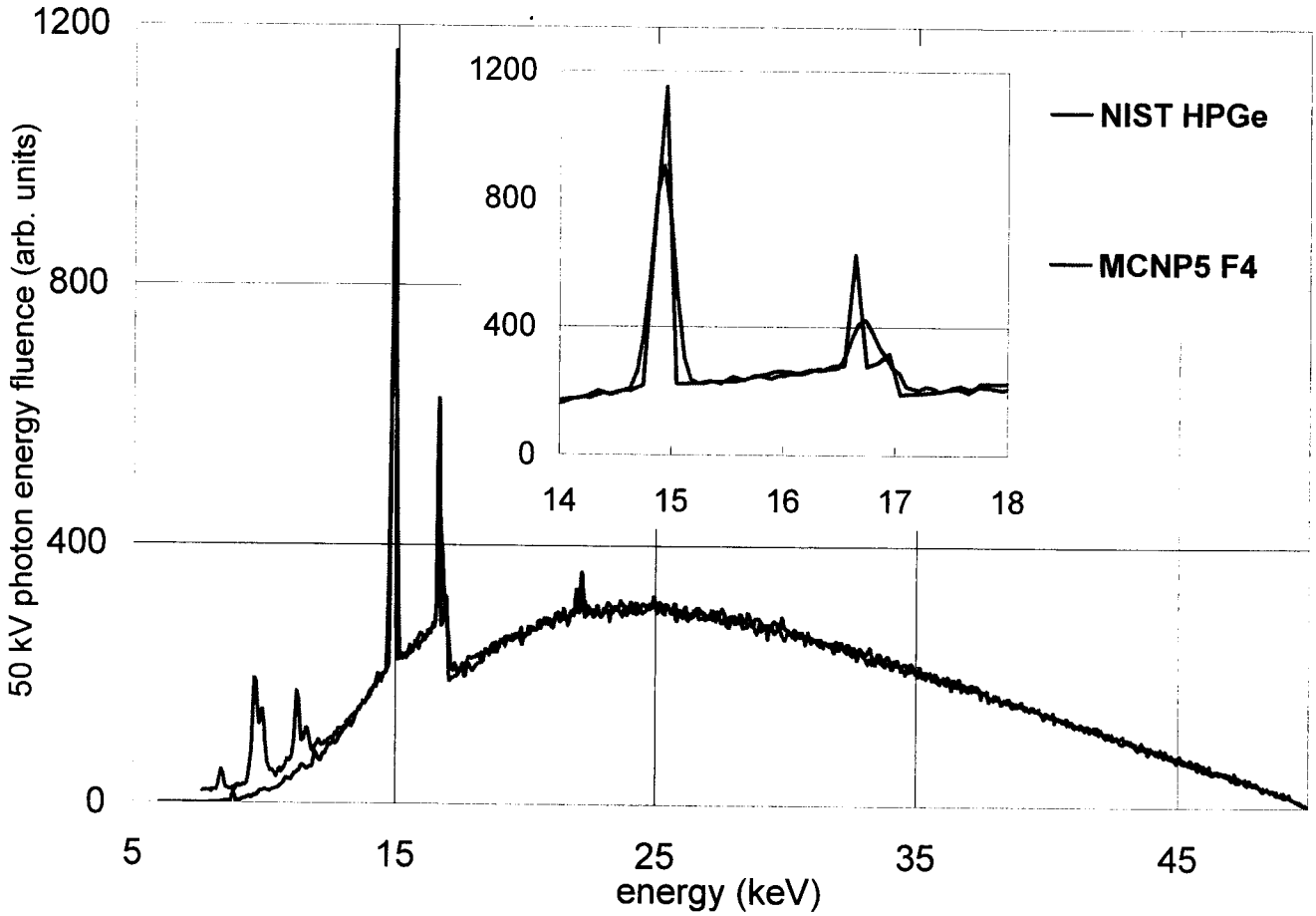


Fig. 4. Relative photon energy spectra at 40, 45, and 50 kV for the model S700 Source along the transverse-plane. Calculations were performed using MCNP version 5 with 100 eV bin widths. Measurements were obtained at NIST using a high-purity germanium (HPGe) detector and 60 eV bin widths for the multi-channel analyzer.

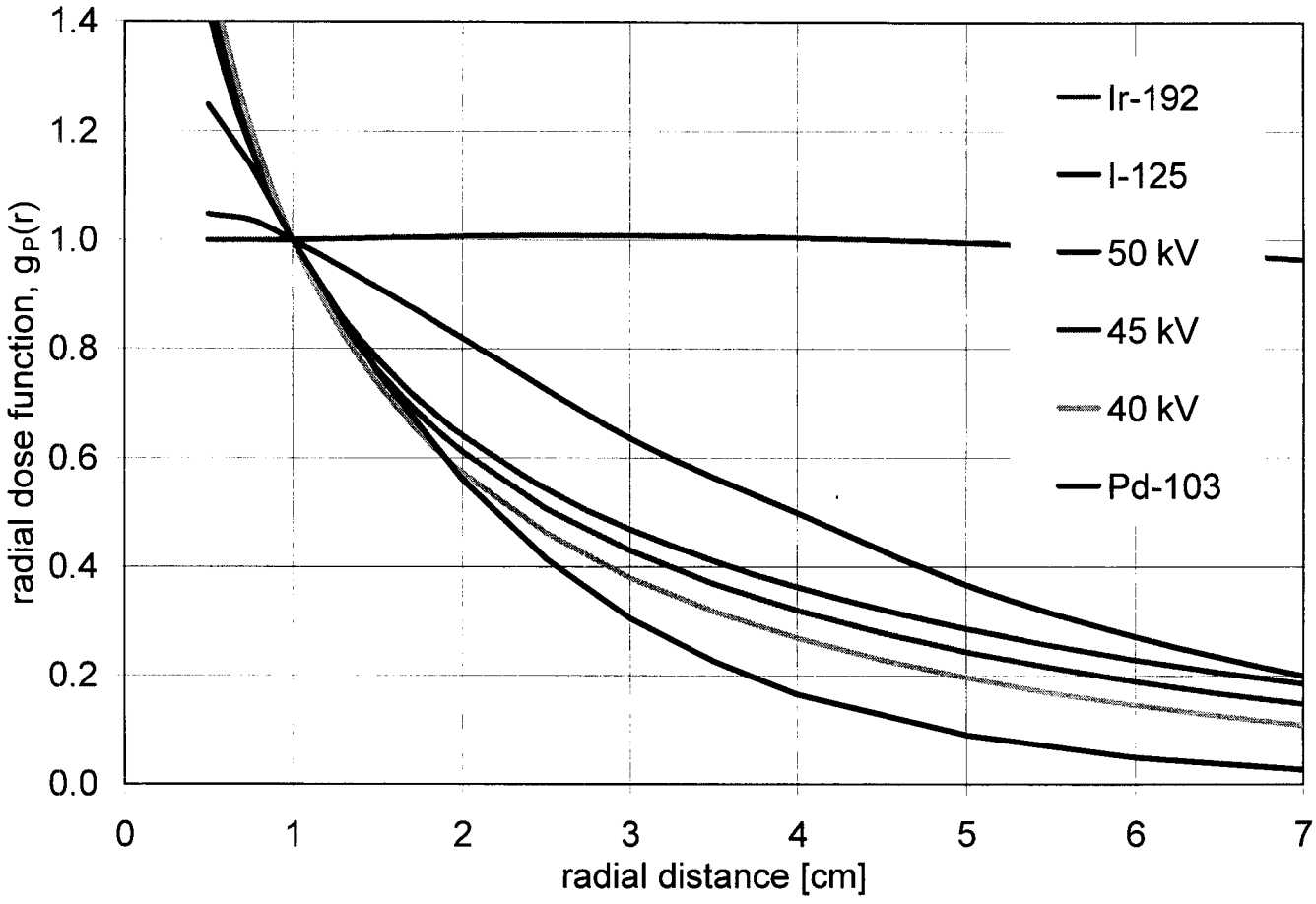


Fig. 5. Radial dose functions for HDR ^{192}Ir, LDR ^{125}I, and LDR ^{103}Pd brachytherapy sources in comparison to those for the model S700 Source at 40, 45, and 50 kV operating voltages. Improved penetration of the model S700 Source as a function of increasing depth is attributed to beam hardening.

ATTACHMENT 7

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 2, pp. 377–381, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.05.042

CLINICAL INVESTIGATION **Breast**

LONG-TERM TOXICITY OF AN INTRAOPERATIVE RADIOTHERAPY BOOST USING LOW ENERGY X-RAYS DURING BREAST-CONSERVING SURGERY

UTA KRAUS-TIEFENBACHER, M.D.,* LELIA BAUER, M.D.,† ANTONELLA SCHEDA, M.D.,* KATHARINA FLECKENSTEIN, M.D.,* ANKE KELLER,* CARSTEN HERSKIND, PH.D.,* VOLKER STEIL, M.SC.,* FRANK MELCHERT, M.D.,† AND FREDERIK WENZ, M.D.*

Departments of *Radiation Oncology and †Gynecology and Obstetrics, Mannheim Medical Center, University of Heidelberg, Mannheim, Germany

Purpose: Intraoperative radiotherapy (IORT) as a boost for breast cancer delivers a high single dose of radiation to a late-reacting tissue; therefore late toxicity is of particular interest, and long-term follow-up is warranted. To date there are only limited data available on breast cancer patients treated with IORT using low energy X-rays. We analyzed toxicity and cosmesis after IORT as a boost with a minimum follow-up of 18 months.

Methods and Materials: A total of 73 patients treated with IORT (20 Gy/50 kV X-rays; INTRABEAM [Carl Zeiss Surgical, Oberkochen, Germany]) to the tumor bed during breast-conserving surgery as a boost followed by whole-breast radiotherapy (WBRT, 46 Gy) underwent a prospective, predefined follow-up (median, 25 months; range 18–44 months), including clinical examination and breast ultrasound at 6-months and mammographies at 1-year intervals. Toxicities were documented using the common toxicity criteria (CTC)/European Organization for Research and Treatment of Cancer and the LENT-SOMA score. Cosmesis was evaluated with a score from 1 to 4.

Results: The IORT in combination with WBRT was well tolerated, with no Grade 3 or 4 skin toxicities and no telangiectasias. Fibrosis of the entire breast was observed in 5% of the patients. A circumscribed fibrosis around the tumor bed was palpable in up to 27% with a peak around 18 months after therapy and a decline thereafter. The observed toxicitiy rates were not influenced by age, tumor stage, or systemic therapy. The cosmetic outcome was good to excellent in ≥90% of cases.

Conclusions: After IORT of the breast using low-energy X-rays, no unexpected toxicity rates were observed during long-term-follow-up. © **2006 Elsevier Inc.**

Intraoperative radiotherapy, Breast cancer, Boost, Late toxicity, Cosmesis.

INTRODUCTION

The therapy of breast cancer has achieved considerable success over the past 2 decades. Whole-breast radiotherapy (WBRT) can reduce the local breast tumor recurrence rate after breast-conserving surgery from 25% to 30% to less than 10% at 10 years (1–4). The results of the European Organization for Research and Treatment of Cancer (EORTC) 22881 study (5) and the Lyon trial (6) showed that the local recurrence rate could be further reduced when a tumor bed boost is given in addition to WBRT in selected patients. For the correct delivery of a boost a precise demarcation of the excision cavity is mandatory. It has been estimated that the externally delivered boost may miss the target volume in approximately 20% to 90% of cases (7, 8). Theoretically, brachytherapeutic or intraoperative approaches for delivering a boost to the tumor bed may be advantageous regarding geographic misses; however late toxicity after a high-irradiation dose per fraction delivered to a late-reacting organ such as the breast is a concern.

Intraoperative radiotherapy (IORT) can be delivered with dedicated linear accelerators in the operation rooms or novel mobile devices using electrons or low-energy X-rays (9–11). There are several reports on interstitial brachytherapy techniques (12–17), but data regarding late toxicity and cosmetic outcome of breast cancer patients treated with IORT are scarce (18, 19). Here we report on late toxicity and cosmetic outcome of breast cancer patients treated in a single institution with IORT using kV X-rays as a boost followed by WBRT.

METHODS AND MATERIALS

A total of 73 patients who were treated consecutively in the Mannheim Medical Center/University of Heidelberg with IORT during BCS between February 2002 and August 2004 were in-

Reprint requests to: Uta Kraus-Tiefenbacher, M.D., Department of Radiation Oncology, Mannheim Medical Center, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel: (+49) 621-383-3530; Fax: (+49) 621-383-3493; E-mail: uta.kraus-tiefenbacher@radonk.ma.uni-heidelberg.de

Received April 11, 2006, and in revised form May 24, 2006. Accepted for publication May 24, 2006.

cluded in this analysis. Eligibility criteria were bioptically proven breast cancer, unifocal on preoperative imaging (mammography and ultrasound), a maximum tumor diameter of 45 mm, and a distance to the skin ≥2 mm. Median patient age was 63.4 years (range, 34.6–83.4 years), and median tumor size was 15 mm (range, 2–45 mm).

The INTRABEAM system (Carl Zeiss Surgical, Oberkochen, Germany) is a mobile, miniature X-ray generator (30–50 kV). Accelerated electrons strike a gold target at the tip of a 10-cm long drift tube with a diameter of 3 mm resulting in an isotropic dose distribution around the tip. Spherical applicators ranging from 1.5 to 5.0 cm in diameter are placed over the drift tube. After surgical removal of the tumor the specimen and the cavity are measured and the drift tube with the appropriate applicator is placed inside the cavity. A purse-string suture is made to adapt the breast tissue to the applicator surface. After the purse string is tightened around the applicator, the skin is everted by distractors to avoid close contact between the skin and the shaft of the applicator. A more detailed description of the device has been published (20).

The median applicator size was 4.5 cm (range, 3.0–5.0 cm) and the median resection margin was 10 mm (range, 1–12 mm). All patients received a dose of 20 Gy per fraction prescribed to the applicator surface. IORT was delivered using the INTRABEAM system with 50 kV X-rays over a median treatment time of 20 min (range, 19–49 min).

Table 1. Characteristics of the 73 intraoperative radiotherapy patients

Age (y)	
≤50	12
51–60	16
61–70	29
71–80	14
≥80	2
Initial tumor size	
T1a	0
T1b	12
T1c	38
T2	23
Histology	
Ductal-invasive	36
Lobular-invasive	18
Tubulo/lobular-invasive	13
Other	6
Grading	
1	14
2	44
3	15
Nodal involvement	
N0	50
N1mic	4
N1a	14
N2a	3
N3a	2
NX	0
Hormone receptors	
Positive	67
Negative	6
Endocrine therapy	
Yes	66
No	7
Chemotherapy	
Yes	18
No	55
EIC + lymphangioinvasion	8
	7

Abbreviation: EIC = extensive intraductal component. Based on TNM-Classification, 6th edition, 2002.

Table 2. CTC/European Organization for Research and Treatment of Cancer score for skin toxicity during and after radiotherapy

Grade 0	None
Grade 1	Slight erythema, epilation, dry desquamation, reduced perspiration
Grade 2	Moderate erythema, sporadic moist epitheliolysis (<50%), moderate edema, local care necessary
Grade 3	Strong erythema, confluent moist epithelioysis (>50%), strong edema, intensive local care necessary
Grade 4	Deep ulceration, necrosis, surgical therapy necessary

Abbreviation: CTC = common toxicity criteria.

All patients were treated with IORT as a boost followed by WBRT with a total dose of 46 Gy after wound-healing or after end of chemotherapy. WBRT was delivered at a linear accelerator with a standard technique including 2 tangential opposed fields with energies ranging from 6 to 18 MV photons. The single dose for all patients was 2.0 Gy delivered 5 times per week. Three-dimensional treatment planning (Oncentra MasterPlan, Nucletron, Veenendaal, The Netherlands) was done for all patients based on computed tomography.

After local treatment 66 patients were treated by endocrine therapy with either tamoxifen or anastrozol. A total of 18 patients had adjuvant chemotherapy according to the following schedules: 13 patients had 4 to 6 cycles of epirubicin (90 mg/m^2)/cyclophphosphamide (600 mg/m^2) (EC) or 3 to 6 cycles 5-fluorouracil (500 mg/m^2)/epirubicin (60 mg/m^2)/cyclophosphamide (500 mg/m^2) (FEC) before WBRT, and 2 patients had 2 to 3 cycles of EC followed by WBRT, then another 2 to 3 cycles of EC or FEC. Two patients had 4 cycles of EC followed by 4 cycles of docetaxel (70 mg/m^2) before WBRT, and 1 patient had 6 cycles of cyclophosphamide (600 mg/m^2)/methotrexate (40 mg/m^2)/5-fluorouracil (600 mg/m^2) (CMF) before WBRT. Relevant patient characteristics are listed in Table 1.

For prospective follow-up all patients had a predefined schedule, which included clinical examination and breast-ultrasound at 6-months and mammographies at 1-year intervals. Skin erythemas were prospectively documented using the common toxicity criteria (CTC)/European Organization for Research and Treatment of Cancer score (21) (Table 2).

A palpable induration of the tumor bed or induration of the entire breast was documented separately according to the LENT-SOMA scale for breast carcinoma radiotherapy (Table 3). Other findings such as breast edema, hyperpigmentation, mastitis, and hematoseroma were documented without grading.

The cosmetic outcome was assessed by 1 to 3 experienced radiooncologists after 6 and 12 months and then yearly, and was

Table 3. LENT-SOMA scale V06, 7/2003, for breast carcinoma radiotherapy: post radiation fibrosis

Grade 0	None
Grade 1	Barely palpable/increased density
Grade 2	Definite increased density and firmness
Grade 3	Marked density, retraction and fixation

documented by standardized digital photography. A scoring system was used that was based on the global cosmetic score developed by Harris *et al.* (22), ranging from 1 to 4 (1 = excellent, 2 = good, 3 = fair, 4 = poor).

Logistic regression was used to calculate the proportion of patients who showed increased toxicitiy by age, tumor stage, and adjuvant therapy. Differences in adjusted proportions were tested between groups with Wald tests.

RESULTS

Toxicity

In general, IORT of the tumor bed in combination with WBRT was well tolerated. After a median follow-up of 25 months no Grade 3 or 4 skin toxicities and no teleangiectasias were observed. Other than 3 patients with Grade 1 erythema 6 months after therapy, no further erythema of any grade was observed.

Two patients were treated with antibiotics because of a mastitis 6 months after BCS. After 6 and 12 months hyperpigmentation of the skin was observed in 2 patients. One patient presented with an edema of the breast after 6 months, which resolved during further follow-up.

Detailed information about the clinical assessment of fibrosis is listed in Table 4. There is no differentiation for subvolumes (e.g., tumor bed vs. whole breast) in the LENT-SOMA scale. However, for the present analysis, we used a differentiation between a localized induration/fibrosis around the tumor bed and a fibrosis of the entire breast. A clinically evident fibrosis around the tumor bed of Grade 1 to 2 occurred in up to 27% (19 patients) and of Grade 3 in 1 patient. Importantly, the fibrotic volumes in some patients slowly began to resolve during longer follow-up starting from 12 months. No patient was observed to have progressing fibrosis over time. A palpable fibrosis of the entire breast was observed only in 3 patients. One patient underwent mastectomy because of a diffuse fibrosis Grade 3 of the entire breast 12 months after BCS; the other patients did not need specific therapy.

There was no statistical difference regarding the documented toxicities because of patient age, applicator size, tumor stage, or systemic treatment.

Cosmesis

The long-term cosmetic outcome of all patients was very reasonable with excellent or good results in more than 90% of patients (Fig. 1). Fair cosmetic results were documented over time in 5% and 10% of patients. At 12-month follow-up 2 patients had a poor cosmetic result. One patient was treated by mastectomy because of a marked breast fibrosis; the cosmetic outcome of the other patient was evaluated as fair during further follow-up because of the mentioned resolution of tumor bed fibrosis.

DISCUSSION

Current irradiation approaches for a tumor bed boost in breast-conserving therapy include external beam radiotherapy, interstitial and intracavitary (balloon) brachytherapy, and IORT. The evaluation of the cosmetic results of 1872 patients of the EORTC boost trial 3 years after treatment (5) showed that an external electron beam boost can worsen the cosmetic outcome. Good or excellent cosmesis was found in 71% of the boost group vs. in 86% of the no-boost group (23). With regard to long-term toxicity after brachytherapy, several studies have reported 13% to 56% fibrosis, 11% to 48% teleangiectasia, and 76% to 90% good or excellent cosmetic results after median follow-ups of 42 to 69 months (12, 14–16). In addition, a recently published analysis of 85 patients treated with interstitial brachytherapy showed 15% asymptomatic fat necroses (17). Long-term outcome data after intracavitary (balloon) brachytherapy have not been reported up to now.

Electron IORT using linear accelerators (Linacs) has been used as an alternative for the boost for many years (24–29). However, there are only scarce data on late toxicity and cosmesis of patients treated with breast IORT,

Table 4. Fibrosis rate: patient numbers and percentages at 6, 18, 24, and 36 months of follow-up

	6 m *n* (%)	12 m *n* (%)	18 m *n* (%)	24 m *n* (%)	36 m *n* (%)
All patients	73	71*	70*†	54	19
Clinically evident tumor bed fibrosis	12 (16)	17 (24)	19 (27)	12 (22)	4 (21)
LENT-SOMA 1	9 (12)	6 (8)	11 (16)	5 (9)	1 (4)
LENT-SOMA 2	3 (4)	10 (14)	8 (11)	7 (13)	3 (16)
LENT-SOMA 3	0	1 (1)	0	0	0
Clinically evident breast-fibrosis	2 (3)	3† (4)	2 (3)	2 (4)	1 (5)
LENT-SOMA 1	0	0	0	0	0
LENT-SOMA 2	2 (3)	1 (1)	1	1 (2)	1 (5)
LENT-SOMA 3	0	2* (3)	2 (3)	1 (2)	0

* Of 3 patients, 2 had adverse events before 12/18 months-follow-up: 1 patient died 12 months after breast-conserving surgery (BCS) with multifocal recurrent disease and diffuse skin metastases, 1 patient died 13 months after BCS caused by distant lung metastases.

† One patient with a marked fibrosis had a mastectomy 12 months after intraoperative radiotherapy and was not listed for further follow-up.

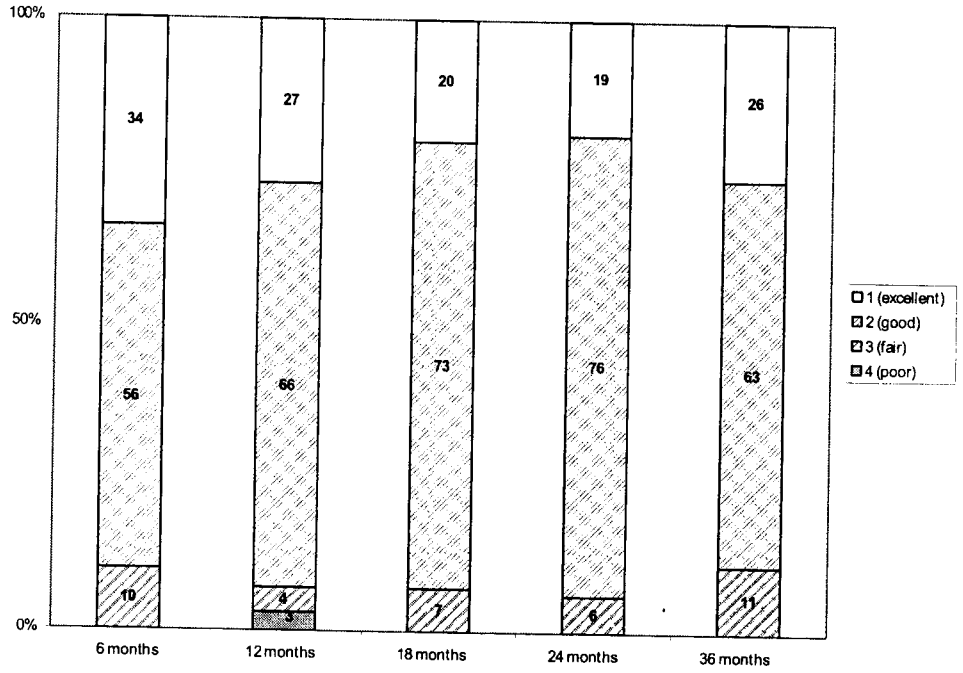


Fig. 1. Cosmetic evaluation after 6, 12, 18, 24, and 36 months on a score of 1 to 4. One patient with a poor cosmetic result was treated with mastectomy because of marked fibrosis of the entire breast 12 months after intraoperative radiotherapy (IORT), and 1 patient was evaluated as having "fair" cosmetic outcome during further follow-up.

although high single doses to late-reacting tissues are of special interest regarding late toxicity. Investigative groups from the United States and France showed that after a median follow-up of 6 and 10 years, breast tissue can tolerate irradiation with 10 Gy in a single fraction followed by a full-course of WBRT with acceptable toxicity and excellent cosmesis. Only mild indurations under the lumpectomy scar and overall excellent cosmetic results (94%) were reported from both groups (24, 25). The recently updated results of both groups have revealed that 10 years after treatment 11% to 14% of the patients from both series developed a delayed fibrosis, which was palpable but not painful (26, 27). No Grade 3 or greater side effects were observed (27). Another group reported that 2 of 190 patients treated with a 9-Gy electron boost before 51 to 56 Gy WBRT developed rib necroses (2%), but no other relevant toxicities were seen (28). Within the Electron intraoperative treatment (ELIOT)-trial, Veronesi *et al.* at the European Institute of Oncology were treating patients with single-fraction IORT alone (21 Gy) using electrons. After a median follow-up of 20 months (range, 4–57) and 590 cases, 3.2% breast fibroses were reported (19, 29). Single cases showed a resolution of the induration during further follow-up.

With the development of mobile, miniature X-ray generators such as the INTRABEAM), a new modality has become available for IORT. The application of kV X-rays for IORT has several logistic advantages especially regarding shielding. However, the radiobiology of low energy X-rays is very complex (30–32), and there are concerns relating to the increased relative biologic effectivity of low-energy X-rays. Radiobiologic modeling has suggested that toxicity rates should be low because of the low-dose-rate when the irradiated volume is limited. Early experience in breast cancer patients was promising (20, 31–33). The first group using IORT alone (15 or 20 Gy) as a replacement for the entire WBRT course treated only 7 patients in a pilot study with 120 KV radiation (Picker Zephyr 120). At a median follow-up of 72 months, no undue toxicity was noted (31). The group from London reported that the cosmetic outcome of 25 boost patients (50 kV X-rays) after a median follow-up of 22 months either matched or exceeded their expected scores in 84% of cases and no major complications were seen (32). In extension of our previous experience with short-term follow-up (33), we have observed, after a median follow-up of 18 months, an acceptable rate of palpable fibroses predominantly of Grades 1 and 2, limited mainly to the tumor bed in a consecutive series of 73 patients treated with 20 Gy IORT boost (50 kV) followed by 46 Gy external beam radiotherapy.

Currently, the international multicenter trial TARGeted Intraoperative radioTherapy (TARGIT) is randomising patients to standard whole-breast radiotherapy (WBRT) vs. IORT using kV X-rays followed by WBRT for patients with certain risk factors only. Because patients without risk factors (size, margins, extensive intraductal component [EIC]) receive IORT to the tumor bed only within the TARGIT trial, one may expect, that the overall toxicity rate because of this risk adapted strategy should even be lower than the numbers reported in the present series where all patients received IORT followed by WBRT.

CONCLUSION

In conclusion, the most frequent side effect of IORT during breast-conserving surgery for early-stage breast can-

cer using low-kV X-rays was a low-grade fibrosis limited to the tumor bed. This was observed in less than 30% of the patients, and a clinically evident fibrosis of the whole breast was seen in less than 5%. The cosmetic results were good or excellent in 90% or more cases. No higher-grade skin toxicities or teleangiectases were observed.

REFERENCES

1. Veronesi U, Marubini E, Mariani L. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol* 2002;12:997–1003.
2. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled analysis for risks of ipsilateral breast tumour recurrence and mortality. *J Natl Cancer Inst* 2004;96:115–121.
3. Fisher B, Anderson S, Bryant J, *et al.* Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233–1241.
4. Veronesi U, Cascinelli N, Mariani L, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–1232.
5. Bartelink H, Horiot JC, Poortmans P, *et al.* Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;345: 1378–1387.
6. Romestaing P, Lehingue Y, Carrie C, *et al.* Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;15:963–968.
7. Machtay M, Lanciano R, Hoffman J, Hanks GE. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 1994; 30:43–48.
8. Benda RK, Yasuda G, Sethi A, *et al.* Breast boost: are we missing the target? A dosimetric comparison of two boost techniques. *Cancer* 2003;97:905–909.
9. Reitsamer R, Peintinger F, Sedlmayer F, *et al.* Intraoperative radiotherapy given as a boost after breast-conserving surgery in breast cancer patients. *Eur J Cancer* 2002;38:1607–1610.
10. Veronesi U, Orrechia R, Luini A, *et al.* Focalised intraoperative irradiation after conservative surgery for early stage breast cancer. *Br J Surg* 10(Suppl. 3):84–89, 2001.
11. Vaidya JS, Tobias JS, Baum M, *et al.* TARGeted Intraoperative radioTherapy (TARGIT): an innovative approach to partial-breast irradiation. *Semin Rad Oncol* 2005;15:84–91.
12. Manning MA, Arthur DW, Schnidt, Ullrich RK, *et al.* Interstitial high-dose-rate brachytherapy boost: the feasibility and cosmetic outcome of a fractionated outpatient delivery scheme. *Int J Radiat Oncol Biol Phys* 2000;48:1301–1306.
13. King TA, Bolton JS, Kuske RR, *et al.* Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for Tis, 1,2 breast cancer. *Am J Surg* 2000;180:299–304.
14. Harms W, Krempien R, Hensley FW, *et al.* 5-Year results of pulsed dose rate brachytherapy applied as a boost after breast-conserving therapy in patients at high risk for local recurrence from breast cancer. *Strahlenther Onkol* 2002;178:607–614.
15. Arthur DW, Koo D, Zwicker R, *et al.* Partial breast brachytherapy after lumpectomy: low-dose-rate and high-dose-rate experience. *Int J Radiat Oncol Biol Phys* 2003;56:681–689.
16. Benitez PR, Chen PY, Vicini FA, *et al.* Partial breast irradiation in breast-conserving therapy by way of interstitial brachytherapy. *Am J Surg* 2004;188:344–364.
17. Ott O, Schulz-Wendtland R, Uter W, *et al.* Fat necrosis after conserving surgery and interstitial brachytherapy and/or external-beam irradiation in women with breast cancer. *Strahlenther Onkol* 2005;181:638–644.
18. Merrick HW 3rd, Hager E, Dobelbower RR Jr. Intraoperative radiation therapy for breast cancer. *Surg Oncol Clin North Am* 2003;12:1065–1078.
19. Veronesi U, Orecchia R, Luini A, *et al.* Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. Experience with 590 cases. *Ann Surg* 2005;242:101–106.
20. Kraus-Tiefenbacher U, Steil V, Bauer L, *et al.* A novel mobile device for intraoperative radiotherapy (IORT). *Onkologie* 2003;26:596–598.
21. Seegenschmidt MH, Sauer R. Systematik der akuten und chronischen Strahlenfolgen. *Strahlenther Onkol* 1993;169: 83–95.
22. Harris JR, Levene MB, Svensson G, *et al.* Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1979;5:257–261.
23. Vrieling C, Collette L, Fourquet A, *et al.* On behalf of the EORTC radiotherapy and breast cancer cooperative groups. The influence of patient, tumour and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC "boost vs. no boost" trial. *Radiother Oncol* 2000;55:219–232.
24. Dobelbower R, Merrick H, Eltaki A, *et al.* Intraoperative electron beam therapy and external photon beam therapy with lumpectomy as primary treatment for early breast cancer. *Ann Radiol (Paris)* 1989;32:497–501.
25. Dubois J, Hay M, Gely S, *et al.* IORT in breast carcinomas. *Front Radiat Ther Oncol* 1997;31:131–137.
26. Merrick HW 3rd, Hager E, Dobelbower R Jr. Intraoperative radiation therapy for breast cancer. *Surg Oncol Clin North Am* 2003;12:1065–1078.
27. Lemanski C, Azria D, Thezenat S, *et al.* Intraoperative radiotherapy given as a boost for early breast cancer: long-term clinical and cosmetic results. *Int J Radiat Oncol Biol Phys* 2006;64:1410–1415.
28. Reitsamer R, Peintinger F, Sedlmayer F, *et al.* Intraoperative radiotherapy given as a boost after breast-conserving surgery in breast cancer patients. *Eur J Cancer* 2002;38:1607–1610.
29. Veronesi U, Gatti G, Luini A, *et al.* Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. *Arch Surg* 2003;138:1253–1256.
30. Herskind C, Steil V, Tiefenbacher U, Wenz F. Radiobiologic aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X-rays for early-stage breast cancer. *Radiat Res* 2005;163:208–215.
31. Proulx GM, Stomper PC, Hurd T, Lee RJ, Podgorsak M, Edge SB. Breast-conserving therapy (BCT): Radiating the entire breast may not be necessary [Letter to the editor]. *Breast J* 2001;7:275.
32. Vaidya J, Baum M, Tobias J, *et al.* TARGeted Intraoperative radioTherapy (TARGIT): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001;12:1075–1080.
33. Kraus-Tiefenbacher U, Bauer L, Kehrer T, *et al.* Intraoperative radiotherapy (IORT) as a boost in patients with early-stage breast cancer—acute toxicity. *Onkologie* 2006;29:77–82.

ATTACHMENT 8

Annals of Oncology 12: 1075–1080, 2001.

Original article

*Targ*eted *i*ntra-operative radio*t*herapy (*Targit*): An innovative method of treatment for early breast cancer

J. S. Vaidya,[1] M. Baum,[1] J. S. Tobias,[2] D. P. D'Souza,[3] S.V. Naidu[3] S. Morgan,[3] M. Metaxas,[3] K. J. Harte,[4] A. P. Sliski[4] & E. Thomson[4]

[1]*Department of Surgery,* [2]*Department of Radiation Oncology,* [3]*Department of Medical Physics, University College London, UK;* [4]*Photoelectron Corporation, Lexington, Massachusetts, USA*

Summary

Introduction: We believe that conservative treatment of early breast cancer may not require radiotherapy that encompasses the whole breast. We present here the clinico-pathological basis for this view, as well as a novel therapeutic approach that allows intra-operative radiotherapy to be safely and accurately delivered to the target tissues in a standard operating theatre.

The rationale: Whole-organ analysis of mastectomy specimens reveals that 80% of occult cancer foci are situated *remote* from the index quadrant. In contrast, over 90% of local recurrences after breast conservative therapy occur *near* the original tumour, even when radiotherapy is not given. Therefore, the remote occult cancer foci may be clinically irrelevant and radiotherapy to the index quadrant alone might be sufficient.

A novel technique: The Photon Radiosurgery System (PRS) is an ingenious portable electron-beam driven device that can typically deliver intra-operative doses of 5–20 Gy, respectively, to 1 cm and 0.2 cm from the tumour bed over about 22 min. The pliable breast tissue – the target – wraps around the source, providing perfect conformal radiotherapy. Being soft X-rays, the dose attenuates rapidly ($\alpha \sim 1/r^3$), reducing distant damage.

Results: In our pilot study of 25 patients (age 30–80 years, T = 0.42–4.0 cm), we replaced the routine post-operative tumour bed boost with *targ*eted *i*ntra-operative radio*t*herapy. There have been no major complications and no patient has developed local recurrence, although the median follow-up time is short, at 24 months.

Conclusion: It is safe and feasible to deliver *targ*eted *i*ntra-operative radio*t*herapy (*Targit*) for early breast cancer. We have begun a randomised trial – the first of its kind – comparing *Targit* with conventional six-week course of radiotherapy. If proven equivalent in terms of local recurrence and cosmesis, it could eliminate the need for the usual six-week course of post-operative radiotherapy.

Key words: breast cancer, breast conserving therapy/surgery, IORT, pilot, randomised trial, targeted intra-operative radiotherapy, Targit

Introduction

Over the past 30 years, there has been a dramatic change in the local management of breast cancer from very radical to more conservative surgical operations, with widespread use of radiotherapy in conjunction with wide local excision of the tumour itself. This shift away from radical surgery has been prompted by randomised clinical trials that have clearly demonstrated that conservative breast surgery followed by radiotherapy is equivalent to more radical procedures in terms of overall survival (EBCTCG 1995) [1]. However, although the outcome is 'conservative' the intention is 'radical' with the radiotherapy fields encompassing virtually all of the tissues previously excised by radical mastectomy. We propose that this approach be reappraised and have already suggested the biological and clinico-pathological basis for avoiding unnecessary treatment to the whole breast* [2]. One part of the rationale for the less radical approach is that in large studies of breast conservative therapy more than 90% of early breast recurrences have been found to occur at the site of the original primary tumour. This is true whether or not radiotherapy is given[3] and whether or not the margins are involved [4]. Furthermore, this is the case in spite of the fact that when mastectomy specimens are examined by detailed radiological-histological correlational methods, small additional invasive or *in situ* cancer foci are found in over 60% of patients, with 80% of these situated remote from the index quadrant. The relative distribution of primary tumour and these foci in the four breast quadrants is significantly different [5]. Hence it appears that these additional cancer foci do not in general give rise to local recurrence which more probably develops from the cells that surround the primary tumour. These may be overtly malignant or morphologically normal, yet capable of malignant progression, as evident by the loss of heterozyocity in these 'normal' cells within the index

* Presented by JSV at the Hong Kong International Cancer Congress, Nov. 1995.

quadrant [6]. We have suggested that the next step is a clinical trial to test whether radiotherapy to the index quadrant alone can achieve as good a local control as radiotherapy to the whole breast [4]. This approach of irradiating the index quadrant alone has been tested in two clinical trials and the results seem to support our hypothesis. The Christie Hospital Trial [7] randomised 708 patients to receive either the standard wide field radiotherapy or a limited field radiotherapy to the index quadrant. They found that overall there was a higher recurrence rate in the latter arm. However when the results were analysed according to the type of the primary tumour, it was found that limited field radiotherapy is inadequate only in infiltrating lobular cancers or cancers with extensive intraductal component (EIC). In the 504 cases of infiltrating duct carcinoma, there was no significant difference in the local recurrence rates of the two arms. In the much smaller (n = 27) Guy's Hospital Study [8], a single continuous application of an iridium-192 implant delivering 55 Gy over 5–6 days replaced the standard radiotherapy regimen including whole breast radiotherapy plus tumour bed boost. The authors found a 20% increase in local recurrence compared with historical controls. However, as discussed in a letter in response to the study [9], it was pointed out that the Biologically Effective Dose (BED) was 20% lower than conventional radiotherapy and this almost completely explained the difference. In addition 12/27 patients were node positive and 15/27 had involved margins – putting these patients at high risk of local recurrence anyway.

The new radiotherapy technique: *Targeted intra-operative radiotherapy (Targit)*

We report here the pilot study approved by the University College London Hospitals Ethics Committee in which a novel method of radiotherapy is used to deliver therapeutic radiation to the tissues around the primary tumour immediately following excision, with a degree of precision impossible with an external beam.

The Photon Radiosurgery System (PRS) developed by the Photoelectron Corporation in Massachusetts, USA is a simple and ingenious device which in essence is a miniature electron-beam driven X-ray source which provides a point source of low energy X-rays (50 kV maximum). The unit is connected, via a low-voltage cable, to a control box housing a rechargeable NiCd battery. Within the unit itself, electrons are produced from a barium oxide thermionic cathode, accelerated to the desired energy (up to 50 kV) by a multi-stage anode, and directed down a 10 cm long, 3.2 mm diameter evacuated drift tube towards a thin-film hemispherical gold target at its tip. The resultant spectrum of X-rays is emitted isotropically. Accurate steering of the electron beam is achieved using two sets of X-Y deflection coils, and by the incorporation of magnetic shielding.

The radiation source can be inserted into the area of interest, to provide intra-operative interstitial irradiation. The physics, dosimetry and early clinical applications of this soft X-ray device have been well studied and the probe has already been used for treatment of malignant brain tumours in man [10, 11], though treatment of breast has not previously been attempted. For use in the breast, the radiation source is surrounded by a conical sheath with a sphere at the tip (see Figures 1, 2 and 3). The sphere is specially designed to produce an accurately calculated uniform dose rate at its surface, enabling delivery of a uniform dose of radiation to a prescribed depth. Since the radiation consists of soft X-rays, the beam is rapidly attenuated to reduce the dose to more distant tissue (Figure 4). Full measurements and calibration are carried out in a water phantom and in materials which simulate the radiation absorption properties of the breast. Depending upon the size of the surgical cavity, various sizes of applicator spheres are available and for each size, the radiation received is proportional to the time the machine is switched on and left *in situ*. The precise dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimise the radiation treatment. The radiation dose at various distances from the cavity margin varies as shown for the simulated assembly in Table 1. For example, a dose of about 5 Gy can be delivered in about 20 min at 1cm from the margins of a 3.5 cm cavity after wide local excision of the tumour.

The whole assembly is small and lightweight (Weight = 1.8 kg, Dimensions: X-ray generator body 7 × 11 × 14 cm; applicator: 16 cm long conical applicator sheath with a 2 to 5 cm applicator sphere at the tip) and hangs

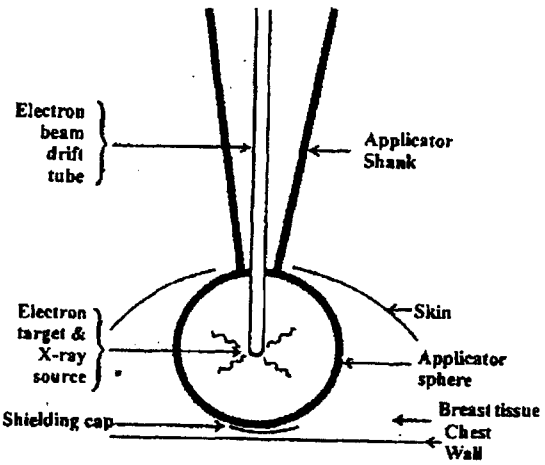


Figure 1. The Photon-Radiosurgery System (PRS). The electrons are generated and accelerated in the main unit (seen in Figure 3) and travel via the electron beam drift tube which is surrounded by the conical applicator sheath such that its tip lies at the epicentre of the applicator sphere. Once the electrons hit the inner surface of the hemisphere at the tip, X-rays are generated. Thus, a uniform radiation dose rate is available at the surface of the applicator sphere. There is a small very high dose region close to the applicator which attenuates quickly ($\alpha \sim 1/r^2$).

Figure 2. The applicator being placed in the tumour bed, immediately after the excision of the tumour.

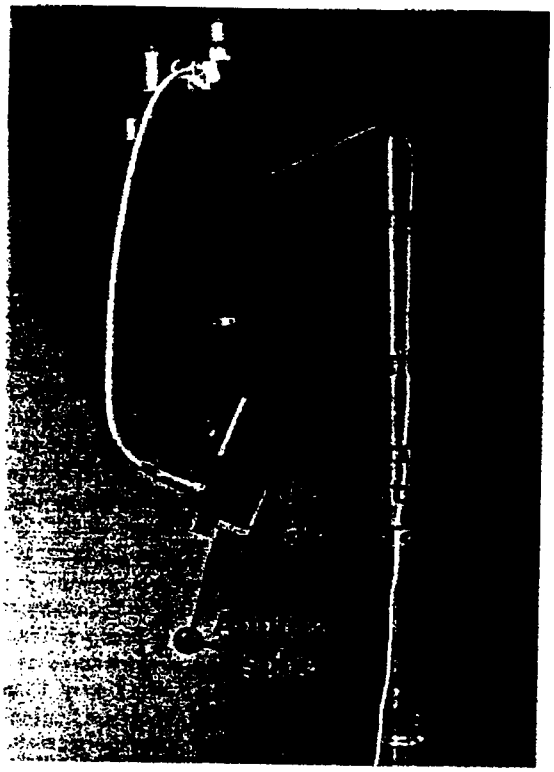


Figure 3. The PRS assembly. The whole assembly is suspended on a counter balance system so that the position of the applicator remains steady irrespective of the respiratory movements. Once the applicator is positioned, the electron beam drift tube with the electron generator and accelerator is inserted in the applicator and maintained by a spring-loaded system.

dependently from a mobile gantry in perfect balance, remaining steady wherever it is positioned. If necessary, the chest wall and skin can be protected (95% shielding) by radio-opaque tungsten-filled polyurethane caps which can be cut to size on the operation table, another advantage of using soft X-rays. With this elegant approach the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source, i.e. the target is 'conformed' to the source. This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of using interstitial implantation of radioactive wires to provide high dose radiotherapy to the tumour bed or the even more complex techniques necessary for conformal radiotherapy by external beams from a linear accelerator. The quick attenuation of the radiation dose allows the treatment to be carried out in unmodified operating theatres. The walls usually incorporate shielding for microwave radiation from electronic equipment such as mobile phones, and provide sufficient staff protection. Furthermore, the biologically effective dose (BED) attenuates rapidly (see Table 1), so that the highest radiation dose is received by tissue nearest the primary tumour and a much lower dose at the skin. Thus in theory, the biological effect and cosmetic outcome could be improved.

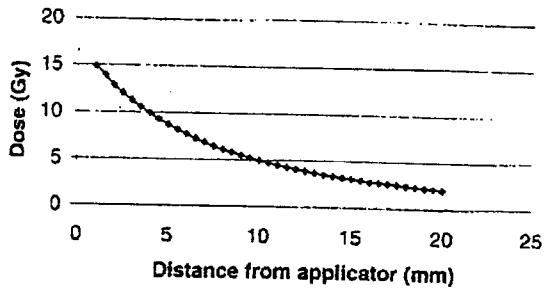


Figure 4. The physical X-ray dose at various distances in a breast phantom for the typical applicator of 3.5 cm diameter and a prescription of 5 Gy at 1 cm.

The operative procedure

Patients who were diagnosed to have operable breast cancer suitable for conservative breast surgery were recruited in the pilot study, after a full informed consent.

Each patient underwent wide local excision and axillary clearance. After haemostasis was achieved, the tumour bed was assessed and the appropriate applicator was attached to the X-ray source (XRS) and inserted in the wound. In the first three cases, the complete PRS device was sterilised. This required the Quality Assurance analysis to be done on the previous day before sterilisation, and repetition in the operating theatre under sterile conditions. From the fourth case onwards, we wrapped up the XRS in a sterile plastic bag, with a hole for the sterile applicator to pass through. Not only has this made the operation streamlined, it has also significantly reduced the time spent by the medical physics team in the operation theatre. Since this modification, the average time required to set-up the

Table 1. Standard dosimetry table. Calculations for a 3.5 cm diameter spherical diameter and a period of irradiation of 21 min as measured from the periphery of the sphere in a breast phantom. (PRS operating parameters: 50 kV). Radial doses are stated for a treatment prescription on 5 Gy at 1 cm.

	PE probe (Gy)		External beam radiotherapy tumour bed boost		Whole breast radiotherapy	
Distance from the surface of the applicator	Physical X-ray dose (Gy)	BED	Physical X-ray dose (Gy)	BED	Physical X-ray Dose (Gy)	BED
0.1 cm	15	165	10	12	50	60
0.2 cm	12.5	121	10	12	50	60
0.5 cm	8.75	59	10	12	50	60
1 cm	5.0	21.7	10	12	50	60

Biologically effective dose (BED) is given by the equation (Dale, 1985 [12]): $BED = D \times (1 + (d/(\alpha/\beta))$ where D is the total physical dose, d is the physical dose per fraction and α/β is the biological coefficient which is 10 for early and tumour effects for tumour tissues when the radiotherapy is delivered in fractions of about 2 Gy. For the single dose we have assumed the value of α/β to be equal to 1.5.

system at the end of excision was only 12 min. When the lesion is on the left side, the chest wall is protected by thin polyurethane-tungsten impregnated sheets that can either be applied to the applicator or custom-made to fit on the chest wall. This reduces the radiation by 95% and protects the heart and coronary vessels. The applicator sphere is inserted into the breast cavity, and a deep surgical purse-string suture is inserted in the subcutaneous plane to bring together the target breast tissue so that it applies well to the surface of the PRS applicator sphere, and holds it in place during radiotherapy (Figures 2 and 3). Our third patient had radionecrosis of the skin close to the scar which we believe was the site of one of these subcutaneous stitches. Since then we have been retracting the skin with 3–0 prolene stitches and ensuring that no part of skin is less than 1 cm from the applicator surface. Essentially these 'conforming' stitches allow real-time hands-on-accurate conformation of the target to the source of radiation. The radiation needs to be switched on for 21 to 28 min depending upon the size of the applicator sphere, and using an energy of 50 kV a dose of 5 Gray (Gy) is delivered at 1 cm distance from the cavity margins. After completion of radiation, the 'conforming' stitches are removed and the skin is sutured in the usual manner with a subcuticular prolene stitch which is left in place for 14 days.

The prescribed dose of 5 Gy at 1 cm (obviously with a much higher dose at the tumour bed margin), was selected as likely to be a safe exposure from a single fraction bearing in mind that the commonest radiotherapy boost programmes provide a small boost of external beam irradiation to a dose of 10 Gy over 5 fractions over a week.

We assessed the cosmetic results of the patients with photographs and by comparing the patient's own assessment of the cosmetic result. We asked the patients to score the appearance and texture of the breast on an analogue scale of 1 to 10, 10 being the best, and the satisfaction index was calculated by dividing the observed by expected.

Results

We began the pilot study on 2 July 1998 and have treated 25 patients. They all had early operable breast cancer, suitable for breast conserving surgery. The age ranged from 30–80 years (mean 51.5). The pathological tumour size ranged from 0.42 cm to 4.0 cm. Twenty-two tumours were infiltrating duct carcinomas (4 grade 1, 7 grade 2 and 11 grade 3) with one of them being the tubular variant and three were invasive lobular carcinomas (2 grade 1, and 1 grade 2). Twenty-two patients had axillary node dissection and three had sentinel node biopsy only. All sentinel nodes were negative and three patients had involved lymph nodes (1, 2 and 1 each). The applicator size was 3.5 cm in 13 cases, 4 cm and 4.5 cm in 4 cases each, 3 cm in 3 cases and 2.5 cm in 1 case. In all except the first case, the operating voltage was 50 kV at 40 microamperes. The mean treatment time required to treat the prescribed dose of 5 Gy at 1 cm was 26.5 min (95% confidence interval (95% CI): 24.3–28.8) The total mean operation time for the wide local excision, axillary clearance and intraopeartive radiotherapy was 1 h 57 min (95% CI: 1 h 47 min – 2 h 7 min). In the first case, we used a 40 kV voltage and took 36.8 min.

Three patients received intraoperative radiotherapy as the only form of radiotherapy. One patient was blind, 80 years old, and keen to avoid daily postoperative visits for external beam radiotherapy. In a joint decision, she was prescribed 7.5 Gy (150% of the usual dose) at 1 cm effectively giving about 23 Gy to the cavity margin as the only radiotherapy. Another patient had a contralateral breast cancer treated 14 years ago with interstitial wire boost and whole breast radiotherapy. In order not to overlap radiation beams in the mid-line, she was prescribed 6 Gy at 1 cm, giving 20 Gy to the cavity margin as the only radiotherapy. The third patient (patient 21 in the pilot study) was a lady who well understood the rationale of our subsequent randomised study and chose not to undergo the five-week course of whole breast radiotherapy, although we had not yet started the randomised trial to test this approach. All other patients

received the routine external beam radiotherapy to the whole breast (50 Gy over 5 weeks).

No patient has had major operative or postoperative complications either in general or in respect of the wound. Two patients had some problem with wound healing and one had wound infection. We believe that one of these was due to excessive radiation and radionecrosis. This was our third patient as mentioned before, who had radionecrosis of a 1 cm area of skin close the applicator. The skin breakdown occurred three months after an initial good healing and resulted in delayed healing by secondary intention. In the 80-year-old blind lady, both the axillary and primary wound had delayed wound healing. Both these patients were very satisfied with the final appearance and/or texture of the breast. In the patient who developed a wound infection, the wound healed satisfactorily within two weeks without delay to her adjuvant treatment. Some short-term erythema around the scar was seen in three patients.

The longest follow up is 35 months, with a median of 24 months and a minimum of 16 months. No patient has had a local recurrence. None of the patients who were eligible (essentially all those who were suitable for breast conserving therapy) have refused to participate in the study. Many patients found the technique logical and could immediately see the practical advantage of fewer visits to the radiotherapy department. The concept of giving the radiotherapy to the tumour bed 'there and then' was also very attractive.

The actual score of appearance of breast and texture of breast, as judged by the patients themselves, either matched or exceeded their expected score in 21 out of 25 patients. At 12–16 months after surgery, the satisfaction index (observed/expected score) was 1.2 (95% CI: 1.1–1.4) for breast appearance, and 1.2 (95% CI: 1.0–1.4) for breast texture.

Discussion

In the present protocol, the PRS was used for boosting the tumour bed in conjunction with external beam irradiation to the whole breast, saving a week of radiotherapy treatment time and travelling for each patient. In those patients undergoing sentinel node excision with immediate frozen section, intra-operative radiotherapy could even be delivered during the time waiting for the frozen section results. In the next phase, we need to test whether giving targeted localised radiotherapy in this manner is equivalent to the routine six-week course of postoperative radiotherapy, since this technique has the potential to save six weeks of external beam radiotherapy time for both the patient and the overstretched resources of radiotherapy departments. In addition, the PRS technique has advantages over other types of brachytherapy. At present, both low-dose-rate and high-dose-rate brachytherapy are employed in order to maximise local dosage for improved local control, but the techniques are time-consuming and expensive. Careful placement of semi-flexible Iridium-192 wires probably represents the 'gold standard' brachytherapy technique at present but geometrical accuracy is important and the implant must be removed at a later date, increasing the workload and creating additional problems of radiation protection. The present technique provides a simple form of brachytherapy, which could potentially provide equivalent benefit with a lesser demand on professional time expended. Although other groups have now started using intra-operative radiotherapy, we believe we are the first to use this approach, and the technique we use is simple, portable, and can be used in a routine operation theatre: yet it achieves excellent dosimetry. The other methods employing massive and expensive linear accelerators can require relocation of the operation theatre in the radiotherapy suite.

We recognise that the follow up of this study is relatively short (median 24 months and longest 35 months) for assessing local recurrence rates, but this was a phase II pilot study mainly testing the feasibility, safety and acceptability of the technique to the patient and not local control, which will be tested in the next phase – the randomised trial. We have already received ethics approval and began, on 29 March 2000, the randomised trial (called *Turgit – Targeted intraoperative radiotherapy*) comparing conventional radiotherapy to radiotherapy delivered to the index quadrant alone, using the PRS (http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+review&uid=9920). This is a pragmatic trial, planned to be a multicentre trial, in which patients suitable for breast conserving therapy undergoing wide local excision and axillary clearance are randomised to either receive the intra-operative radiotherapy only, or the usual six-week course of post-operative radiotherapy. If on final histopathology, the tumour is found to be lobular cancer or harbours extensive intraductal component (>25%, EIC), then they will receive in addition, a course of post-operative whole breast radiotherapy, excluding the tumour bed boost.

In the pilot study we only had one patient with a positive margin – the deep margin. Since this was the blind lady who had received the higher (7.5 Gy at 1 cm) dose of radiotherapy, the area adjacent to the tumour bed would have received about 23 Gy, which was thought to be adequate therapy, and a decision to give no further treatment was taken jointly in the multidisciplinary meeting and with the patient. In the randomised trial, the protocol includes the provision to re-excise those patients with grossly positive margins, and to re-irradiate the revised tumour bed if they were randomised to the intra-operative radiotherapy arm. Previous intra-operative radiotherapy should not contra-indicate this because the previously radiated area would have been excised in the re-excision.

Future implications

The national and international implications of avoiding a six-week course of external beam radiotherapy for early breast cancer would be considerable. Treatment of breast carcinoma often represents a third or more of the total case-load of radiotherapy units worldwide. Many women from the developing world and remote areas of the developed world (e.g. Outback of Australia) cannot benefit from breast conserving therapy because of the large distances between their home and the radiotherapy centre. All too frequently they have to choose mastectomy because they cannot stay in or travel daily to the metropolis for the six weeks of post-operative radiotherapy. If proven equal to the standard treatment, the novel approach would allow these women to have breast-conserving therapy in one sitting. For more privileged women, the avoidance of six weeks of daily visits to a radiotherapy centre would still be a great advantage. Furthermore, in our pilot study we have found that in terms of operational expenses the novel technique needs about three man-hours and 45 min each of operation theatre time and patient time. The conventional six-week course of post-operative radiotherapy on the other hand, costs about nine man-hours, six hours of radiotherapy room time and 30–60 h of patient time. If the cost of conventional radiotherapy is £5000, considering only the 66% saving of man-hours the novel technique would save £3750 per patient. So if we assume that 60% of the 27000 breast cancer patients diagnosed every year in the UK are treated by conservative surgery, the novel technique could potentially save over £60 million (0.60 × 27000 × 3750) per year for the NHS. *In addition*, the saving of expensive resource time on linear accelerators would of course be very substantial.

Acknowledgements

We wish to thank Mr Michael Douek, for comments on the manuscripts and Ms Vardhini Vijay for helping with illustrations.

Funding

The project is funded by the University College London Hospitals Trust and the Photoelectron Corporation.

Conflict of interest

Professor Michael Baum is on the scientific advisory committee of the Photoelectron Corporation (PeC). with share options. Dr Jayant S. Vaidya was partly funded by the Research Grant from Photoelectron Corporation. Ken Harte, Alan Sliski and Euan Thomson are employees of the Photoelectron Corporation.

References

1. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med 1995; 333: 1444–55.
2. Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. Lancet 1997; 349: 208.
3. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. Sem Surg Oncol 1992; 8: 161–6.
4. Vaidya JS, Baum M. Clinical and biological implications of the Milan Breast conservation trials. Eur J Cancer 1998; 34: 1143–4.
5. Vaidya JS, Vyas JJ, Chinoy RF et al. Multicentricity of breast cancer: Whole organ analysis and clinical implications. Br J Cancer 1996; 74: 820–4.
6. Deng G, Lu Y, Zlotnikov G et al. Loss of heterozygosity in normal tissue adjacent to breast carcinomas. Science 1996; 274: 2057–9.
7. Ribeiro GG, Magee B, Swindell R et al. The Christie Hospital breast conservation trial: An update at eight years from inception. Clin Oncol (R Coll Radiol) 1993; 5: 278–83.
8. Fentiman IS, Poole C, Tong D et al. Inadequacy of iridium implant as sole radiation treatment for operable breast cancer [see comments]. Eur J Cancer 1996; 32A: 608–11.
9. Dale RG, Jones B, Price P. Comments on inadequacy of iridium implant as sole radiation treatment for operable breast cancer. Fentiman et al. Eur J Cancer 1996; 32A: 608–11: Eur J Cancer 1997; 33: 1707–8.
10. Cosgrove GR, Hochberg FH, Pardo FS et al. Interstitial irradiation of brain tumors using a miniature radiosurgery device: Initial experience. Neurosurgery 1997; 40: 518–25.
11. Douglas RM, Beatty J, Gall K et al. Dosimetric results from a feasibility study of a novel radiosurgical source for irradiation of intracranial metastases. Int J Radiat Oncol Biol Phys 1996; 36: 443–50.
12. Dale RG. The application of the linear quadratic dose effect equation to fractionated and protracted radiotherapy. Br J Radiol 1985; 58: 515–28.

Received 30 December 2000; accepted 2 April 2001.

Correspondence to:
Dr Jayant S. Vaidya, FRCS, MS, DNB
Academic Department of Surgery
University College London
67–73 Riding House Street
London W1W 7EJ, UK
E-mail: j.vaidya@ucl.ac.uk

ATTACHMENT 9

Coalition For The Advancement Of Brachytherapy

660 Pennsylvania Avenue, S.E.
Suite 201
Washington, D.C. 20003
(202) 548-2307
Fax: (202) 547-4658

April 27, 2005

Don Thompson
Director, Outpatient Care Division
Centers for Medicare and Medicaid Services
Mail Stop C4-01-27
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: Clarification of Billing for Brachytherapy Sources

Dear Mr. Hart:

The Coalition for the Advancement of Brachytherapy (CAB) has been working with CMS for several years to assist in Medicare reimbursement policies on brachytherapy. This letter requests your assistance in clarifying a CMS Program Transmittal on billing for prostate brachytherapy sources in the hospital outpatient setting.

In brief, a December 19, 2003 Medicare Program Transmittal (Transmittal 32, Change Request 3007, Publication 100-20) appeared to instruct hospitals to bill for prostate brachytherapy sources used, while prior CMS policy has made clear that hospitals can bill for sources that the physician has actually ordered.

Specifically, in the fall of 2001, CMS (then HCFA) issued on its Medlearn website Frequently Asked Questions, including the following:

> Q. 114 Can hospitals bill for all brachytherapy seeds ordered by the physician even if the physician does not use all of the brachytherapy seeds?
>
> A. 114 **Yes. There may be times when a physician orders more brachytherapy seeds than necessary since the physician may not know the exact amount of brachytherapy seeds needed for one patient. In this case, the hospital may bill for all of the brachytherapy seeds ordered.**

We agree with this clarification and were concerned when CMS issued the January 2004 Hospital Outpatient Prospective Payment System Update that appeared to restrict hospitals to only bill for seeds actually used (see section below which is underscored from December 19, 2003 Medicare Program Transmittal 32):

> January 2004 Update of the Hospital Outpatient Prospective Payment System (OPPS)
>
> "7. Payment for Prostate Brachytherapy In 2003, CMS paid a packaged amount for prostate brachytherapy. Hospitals were required to bill using HCPCS code G0256 (prostate brachytherapy with palladium sources), when palladium sources were implanted, and HCPCS code G0261 (prostate brachytherapy with iodine sources). These HCPCS codes were to be used in lieu of separate billing for CPT codes 77778 (interstitial radiation source application; complex) and 55859 (transperineal placement of needles or catheters into prostate for interstitial radiation element application, with or without cystoscopy), and HCPCS codes C1718 (iodine sources) and C1720 (palladium sources).
>
> Under the OPPS for 2004, HCPCS codes G0256 and G0261 are deleted. For services furnished on or after January 1, 2004, hospitals are to use the CPT codes 77778 and 55859 to bill for the procedures and HCPCS codes C1718 and C1720 to bill for the brachytherapy sources. Separate payments will be made for the procedures and for the sources. Hospitals are to bill the brachytherapy sources showing the number of sources used in the units column. For example, if 100 brachytherapy sources are implanted in the prostate, the hospital will bill 100 units of the applicable code for the brachytherapy source."

This final section could be misconstrued by hospitals to limit billing to only prostate brachytherapy sources used, even if the physician ordered in good faith what he/she believed to be necessary for the clinical needs of the patient, and the hospital, following the doctor's order, purchased a higher amount. Hospitals should not be penalized for following a physician's order.

Thus, we would ask CMS in its next OPPS update to republish the 2001 Frequently Asked Question number 114, or otherwise clarify that the policy of billing all types of brachytherapy sources actually ordered remains consistent, notwithstanding the December 19, 2003 reference to sources "used".

Please feel free to contact Gordon Schatz, Esq. at (202) 414-9259 if you have additional questions. Thank you for your consideration. We look forward to hearing from you.

Sincerely,

Michael Krachon
Chair

Raymond Horn
Vice-Chair

ATTACHMENT 10

Coalition For The Advancement Of Brachytherapy
660 Pennsylvania Avenue, S.E.
Suite 201
Washington, D.C. 20003
(202) 548-2307
Fax: (202) 547-4658

May 20, 2004

Cindy Read
Director, Outpatient Care Division
Centers for Medicare and Medicaid Services
Mail Stop C4-05-17
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: Clarification of Billing for Brachytherapy Sources

Dear Ms. Read:

As you know, the Coalition for the Advancement of Brachytherapy (CAB) has been working with CMS for several years to assist in Medicare reimbursement policies on brachytherapy. This letter requests your assistance in clarifying a recent CMS Program Transmittal on billing for prostate brachytherapy sources in the hospital outpatient setting.

In brief, a December 19, 2003 Medicare Program Transmittal (Transmittal 32, Change Request 3007, Publication 100-20) appeared to instruct hospitals to bill for prostate brachytherapy sources used, while prior CMS policy has made clear that hospitals can bill for sources that the physician has actually ordered.

Specifically, in the fall of 2001, CMS (then HCFA) issued on its Medlearn website Frequently Asked Questions, including the following:

> Q. 114 Can hospitals bill for all brachytherapy seeds ordered by the physician even if the physician does not use all of the brachytherapy seeds?
>
> A. 114 **Yes. There may be times when a physician orders more brachytherapy seeds than necessary since the physician may not know the exact amount of brachytherapy seeds needed for one patient. In this case, the hospital may bill for all of the brachytherapy seeds ordered.**

We agree with this clarification and were concerned when CMS issued the January 2004 Hospital Outpatient Prospective Payment System Update that appeared to restrict hospitals to only bill for seeds actually used (see section below which is underscored from December 19, 2003 Medicare Program Transmittal 32):

> January 2004 Update of the Hospital Outpatient Prospective Payment System (OPPS)
>
> "7. Payment for Prostate Brachytherapy In 2003, CMS paid a packaged amount for prostate brachytherapy. Hospitals were required to bill using HCPCS code G0256 (prostate brachytherapy with palladium sources), when palladium sources were implanted, and HCPCS code G0261 (prostate brachytherapy with iodine sources). These HCPCS codes were to be used in lieu of separate billing for CPT codes 77778 (interstitial radiation source application; complex) and 55859 (transperineal placement of needles or catheters into prostate for interstitial radiation element application, with or without cystoscopy), and HCPCS codes C1718 (iodine sources) and C1720 (palladium sources).
>
> Under the OPPS for 2004, HCPCS codes G0256 and G0261 are deleted. For services furnished on or after January 1, 2004, hospitals are to use the CPT codes 77778 and 55859 to bill for the procedures and HCPCS codes C1718 and C1720 to bill for the brachytherapy sources. Separate payments will be made for the procedures and for the sources. Hospitals are to bill the brachytherapy sources showing the number of sources used in the units column. For example, if 100 brachytherapy sources are implanted in the prostate, the hospital will bill 100 units of the applicable code for the brachytherapy source."

This final section could be misconstrued by hospitals to limit billing to only prostate brachytherapy sources used, even if the physician ordered in good faith what he/she believed to be necessary for the clinical needs of the patient, and the hospital, following the doctor's order, purchased a higher amount. Hospitals should not be penalized for following a physician's order.

Thus, we would ask CMS in its next OPPS update to republish the 2001 Frequently Asked Question number 114, or otherwise clarify that the policy of billing all types of brachytherapy sources actually ordered remains consistent, notwithstanding the December 19, 2003 reference to sources "used".

Please feel free to contact Gordon Schatz, Esq. at (202) 414-9259 if you have additional questions. Thank you for your consideration. We look forward to hearing from you.

Sincerely,

Michael Krachon
Chair

Raymond Horn
Vice-Chair

ATTACHMENT 11

Coalition For The Advancement Of Brachytherapy

660 Pennsylvania Avenue, S.E.
Suite 201
Washington, D.C. 20003
(202) 548-2307
Fax: (202) 547-4658

September 19, 2005

James Hart
Director, Outpatient Care Division
Hospital and Ambulatory Payment Group
Centers for Medicare and Medicaid Services
Mail Stop C4-07-07
7500 Security Boulevard
Baltimore, MD 21244

Re: Clarification of Billing for Brachytherapy Sources

Dear Mr. Hart:

The Coalition for the Advancement of Brachytherapy (CAB) has been working with CMS for several years to assist in Medicare reimbursement policies on brachytherapy. This letter requests your assistance in clarifying a CMS Program Transmittal on billing for prostate brachytherapy sources in the hospital outpatient setting.

In brief, a December 19, 2003 Medicare Program Transmittal (Transmittal 32, Change Request 3007, Publication 100-20) appeared to instruct hospitals to bill for prostate brachytherapy sources used, while prior CMS policy has made clear that hospitals can bill for sources that the physician has actually ordered.

Specifically, in the fall of 2001, CMS (then HCFA) issued on its Medlearn website Frequently Asked Questions, including the following:

> Q. 114 Can hospitals bill for all brachytherapy seeds ordered by the physician even if the physician does not use all of the brachytherapy seeds?
>
> A. 114 **Yes. There may be times when a physician orders more brachytherapy seeds than necessary since the physician may not know the exact amount of brachytherapy seeds needed for one patient. In this case, the hospital may bill for all of the brachytherapy seeds ordered.**

We agree with this clarification and were concerned when CMS issued the January 2004 Hospital Outpatient Prospective Payment System Update that appeared to restrict hospitals to only bill for seeds actually used (see section below which is underscored from December 19, 2003 Medicare Program Transmittal 32):

> January 2004 Update of the Hospital Outpatient Prospective Payment System (OPPS)
>
> "7. Payment for Prostate Brachytherapy In 2003, CMS paid a packaged amount for prostate brachytherapy. Hospitals were required to bill using HCPCS code G0256 (prostate brachytherapy with palladium sources), when palladium sources were implanted, and HCPCS code G0261 (prostate brachytherapy with iodine sources). These HCPCS codes were to be used in lieu of separate billing for CPT codes 77778 (interstitial radiation source application; complex) and 55859 (transperineal placement of needles or catheters into prostate for interstitial radiation element application, with or without cystoscopy), and HCPCS codes C1718 (iodine sources) and C1720 (palladium sources).
>
> Under the OPPS for 2004, HCPCS codes G0256 and G0261 are deleted. For services furnished on or after January 1, 2004, hospitals are to use the CPT codes 77778 and 55859 to bill for the procedures and HCPCS codes C1718 and C1720 to bill for the brachytherapy sources. Separate payments will be made for the procedures and for the sources. Hospitals are to bill the brachytherapy sources showing the number of sources used in the units column. For example, if 100 brachytherapy sources are implanted in the prostate, the hospital will bill 100 units of the applicable code for the brachytherapy source."

This final section could be misconstrued by hospitals to limit billing to only prostate brachytherapy sources used, even if the physician ordered in good faith what he/she believed to be necessary for the clinical needs of the patient, and the hospital, following the doctor's order, purchased a higher amount. Hospitals should not be penalized for following a physician's order.

Thus, we would ask CMS in its next January 2006 OPPS update to republish the 2001 Frequently Asked Question number 114, or otherwise clarify that the policy of billing all types of brachytherapy sources actually ordered remains consistent, notwithstanding the December 19, 2003 reference to sources "used".

Please feel free to contact Gordon Schatz, Esq. at (202) 414-9259 if you have additional questions. Thank you for your consideration. We look forward to hearing from you.

Sincerely,

Raymond Horn
Chair

Lisa Hayden
Vice-Chair