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● *Clinical Investigation*

MUSCLE INVASIVE BLADDER CANCER TREATED BY TRANSURETHRAL RESECTION, FOLLOWED BY EXTERNAL BEAM RADIATION AND INTERSTITIAL IRIDIUM-192

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Purpose: To evaluate the results of transurethral resection (TUR), external beam radiotherapy (EBRT), and interstitial radiation (IRT) with iridium-192, using the afterloading technique in patients with muscle invasive bladder cancer.

Methods and Materials: From May 1989 until September 1995, 66 patients with primary, solitary muscle invasive bladder cancer were treated with TUR, EBRT, and IRT, aiming at bladder preservation. According to the protocol, in three patients low-dose EBRT was applied, whereas 63 patients received high-dose EBRT. Immediately prior to IRT, 42 patients underwent a lymphnode dissection, and in 16 cases a partial cystectomy was performed. For IRT, two to five catheters were used and IRT was started within 24 h after surgery. The majority of patients received 30 Gy of IRT, with a mean dose rate of .58 Gy/h. In three patients, additional EBRT was applied following IRT. Follow-up consisted of regular cystoscopies, mostly done during joint clinics of urologist and radiation oncologist, with urine cytology routinely performed. The median follow-up period was 26 months. The Kaplan-Meier method was used for the determination of survival rates.

Results: In seven patients, a bladder relapse developed. The probability of remaining bladder relapse free at 5 years was 88%. The bladder was preserved in 98% of the surviving patients. Metastases developed in 16 patients, and the probability of remaining metastasis free at 5 years was 66%. The cumulative 5-year overall and bladder and distant relapse free survival were 48% and 69%, respectively. Acute toxicity was not serious in the majority of cases; surgical correction of a persisting vesicocutaneous fistula was necessary in two patients, whereas a wound toilet had to be performed in another patient. Serious late toxicity (bladder, RTOG Grade 3) was experienced by only one patient.

Conclusions: Interstitial radiation preceded by TUR and EBRT, in a selected group of patients with muscle invasive bladder cancer, yields an excellent bladder tumor control rate with a high probability of bladder preservation. Survival was mainly dependent on the development of distant metastases. Serious acute and late toxicity was rare. © **1997 Elsevier Science Inc.**

Bladder cancer, Interstitial radiation, Bladder preservation.

INTRODUCTION

To our knowledge, the idea of interstitial radiotherapy (IRT) for tumors by radium was developed in Paris in the first decade of the 20th century. Shortly afterwards, reports emerged from several centers in Europe and the United States of America concerning IRT in bladder cancer by permanent implantation of radon seeds (2, 12, 21, 23, 30, 52) or gold grains (8, 32, 55), or by temporary insertion of radium needles (8, 10, 21, 24, 27, 43) or cobalt needles (38), or of tantalum wires (5, 38, 51, 55), or iridium wires (35). Obviously, the radiation hazard of these methods was a serious disadvantage. This problem could be solved by the development of an afterloading system using iridium wires, which was first described in 1969 (19). To date, the iridium afterloading technique is considered standard in IRT in bladder cancer (3, 31, 34, 37).

At the Dr. Daniel den Hoed Cancer Center radium needles were introduced in the treatment of bladder cancer in 1951; they were replaced by caesium needles in 1983, whereas the afterloading iridium wire technique was adopted in 1989. Besides the reduction in radiation

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exposure, this technique offers the opportunity of dose optimization to some extent by choosing wires of different activity or by using different application times within the implanted volume. Pulsed-dose rate (PDR) brachytherapy using a single iridium source "stepping" through a range of dwell positions is a new type of IRT simulating a continuous low-dose rate (LDR) treatment by a series of fractions (pulses) of short duration with time intervals between fractions of 1 h to a few h (7). In PDR, optimization of dose distribution is possible by dwell time variations (26).

By regular evaluation of IRT results and exploration of the role of several schemes of additional external beam radiotherapy (EBRT) and of prognostic factors (44–49), for patients with solitary bladder cancer with a limited surface diameter (<5 cm), the following treatment policy was developed at our center: T1 tumors: IRT 60 Gy, T2 tumors without adverse prognostic factors: EBRT 3 × 3.5 Gy followed by IRT 60 Gy, T2 tumors with adverse prognostic factors (e.g. poorly differentiated, vascular invasion, ureter obstruction), and T3 tumors: EBRT 20 × 2.0 Gy in conjunction with IRT 30 Gy.

In this article we present our first experience in afterloading IRT preceded by EBRT in patients with muscle invasive bladder cancer.

METHODS AND MATERIALS

Patient population

From May 1989 until September 1995, 66 patients with primary, solitary muscle invasive bladder cancer were treated by transurethral resection (TUR), followed by EBRT in conjunction with IRT at the Dr. Daniel den Hoed Cancer Center (DDHCC). As mentioned above, patients with a tumor surface diameter of less than 5 cm were considered for this bladder preserving procedure. Other conditions for this treatment were the possibility to cover the tumor area sufficiently by a one-plane implant and a patient condition permitting surgery. In general, the decision concerning final treatment following TUR was made after a joint evaluation of the patient by the referring urologist and the radiation oncologist. Patient and tumor characteristics are shown in Table 1.

Table 1. Patient and tumor characteristics

Number of patients	66
Sex	
Male	50
Female	16
Age	
Mean	67
Range	36–82
Histology	
Transitional cell carcinoma	63
Squamous cell carcinoma	2
Adenocarcinoma	1
Grade	
1	1
2	9
3	55
4	1
Structure	
Papillary	12
Solid	21
Papillary and solid	20
Not given	13
Depth of infiltration	
Muscle, superficial	12
Muscle, deep	3
Muscle, not specified	50
Perivesical fat	1
T-category*	
T2	62
T3a	3
T3b	1
Site	
Dome	8
Right lateral wall	21
Left lateral wall	13
Posterior wall	7
Anterior wall	2
Right ureter ostium	7
Left ureter ostium	4
Bladder neck	4
Urography/sonography	
No obstruction	40
Unilateral obstruction	7
Not performed	19
Lymph node staging	
Computer tomography	51
Surgery	1
Not performed	14

* TNM classification 1987, 4th edition.

The T-category was defined before definitive treatment according to the 1987 TNM classification (22). In one case, the T2 tumor was multiple. Urography or abdominal sonography revealed a normal upper urinary tract in 40 patients, whereas in 7 patients a unilateral obstruction was observed; no information was available in the remaining 19 patients.

Lymphnode staging by computer tomography (CT) was performed in 51 patients showing no metastases. In one case, a lymphnode dissection was carried out during surgery for an aneurysm of the abdominal aorta before a decision was taken concerning definitive treatment of the bladder tumor; no metastases were found on histological examination. In the remaining 14 patients no information was sought on the nodes.

Treatment

All patients were first treated by TUR of visible tumor. According to our protocol, in three cases 10.5 Gy EBRT (3 × 3.5 Gy) was applied immediately prior to IRT, whereas 62 patients received 40 Gy EBRT (20 × 2.0 Gy) 3 to 42 days (median 13) preceding IRT; in one patient an additional fraction of 2.0 Gy was given to compensate for treatment interruption. The EBRT target area was the true pelvis, radiation being given through opposed anterior and posterior fields (dose calculation in the midplane) in 63

Table 2. Partial cystectomy following EBRT, pathological T-category

Pathological T-category	No. of patients (%)
pT0	8 (50)
pTx	1 (6)
pT1(is)	1 (6)
pT3a	3 (19)
pT3b	3 (19)
Total	16 (100)

patients; in three cases a CT based multiple field planning was used.

Surgery and insertion of catheters for IRT was performed under epidural anesthesia in 62 patients, whereas in 4 patients general anesthesia was given.

A lymphnode dissection of the obturator fossa was performed immediately before the insertion of the catheters for IRT, in 42 patients (38 unilaterally and 4 bilaterally); metastases were found in 3 of them (7%). It was at the discretion of the urologist involved whether a lymphnode dissection was to be performed or not.

To facilitate the positioning of the catheters, in 14 patients an excision of the tumor area (partial cystectomy) was performed, in 2 of them combined with the reimplantation of a ureter and in 1 in combination with a nephrectomy. In another two patients a partial cystectomy had to be performed first, because the tumor process appeared to be too large to perform the originally planned procedure. The partial cystectomy was preceded by 40 Gy EBRT in 15 patients and by 10.5 Gy EBRT in 1 patient. The initial T-category in this subgroup of patients was T2 in 15 patients and T3b in 1 patient. Histological examination showed no residual tumor (pTo) (n = 8), devitalized tumor cells (pTx) (n = 1), superficially infiltrating tumor and concomitant carcinoma in situ (pT1(is)) (n = 1), deep muscle infiltrating tumor (pT3a) (n = 3), and tumor infiltrating perivesical fat (pT3b) (n = 3). In the latter three cases the resection was not radical. In the one T3b patient of this group no residual tumor was found after 40 Gy EBRT. Table 2 shows the pT-categories. The catheters for IRT were inserted at the resection margins after repair of the defect.

In the patients in whom a partial cystectomy was not considered necessary, the bladder was opened in the midline of the anterior wall, unless the tumor site required a paramedian incision, and catheters were inserted parallel to each other, 1–1.5 cm apart, covering the target area, the outer two positioned just outside the area to be irradiated. In one patient a second tumor was discovered at the time of implantation; after resection it was decided to treat this area with IRT also. Because at histopathological examination it appeared to be a T1 tumor, data concerning management of this second tumor in one patient are not included in further analyses. The ends of the catheters were threaded through the abdominal wall separately at both sides lateral to the incision and before the bladder and the abdominal wall were closed, the exact length and position of the iridium wires that were to be used were defined.

After completion of the operation orthogonal radiographs were made of the implanted area and after digitizing of these radiographs, dose distributions were calculated (Figs. 1 and 2). The isodose best encompassing the target area was chosen to calculate the actual application time using the activity of the available iridium wire.

The number of catheters used varied from two to five (two: n = 11; three: n = 38; four: n = 16; five: n = 1).

The mean total length of iridium per patient was 14 cm (range 7 to 27 cm).

According to the protocol, 10.5 Gy EBRT was applied in three patients, in one patient followed by 60 Gy IRT, as planned. The two other patients, however, did not receive the full course (60 Gy) of IRT; in one patient interstitial radiation was terminated after 30 Gy because of unsatisfactory dose distribution, whereas in the other patient we decided to stop IRT after 37.2 Gy because lymphnodes, removed prior to insertion of the catheters, appeared to contain metastases at definitive pathological examination. In both cases, additional courses of 30 and 40 Gy EBRT were applied, respectively.

Following 40 Gy EBRT (in one case 42 Gy), as prescribed by the protocol, an intended IRT dose of 30 Gy was applied in 55 patients, 4 patients received a dose of 35 Gy and 2 patients received 24 and 32.5 Gy, respectively. Because of postoperative mental distress and confusion, IRT was terminated after 26.4 and 16.6 Gy in 2 patients; in the latter case, an additional EBRT dose of 12 Gy was applied. Sequence and doses of EBRT and IRT are summarized in Table 3.

Optimization of dose distributions was considered necessary in 11 implants (17%); in 6 implants iridium wires of

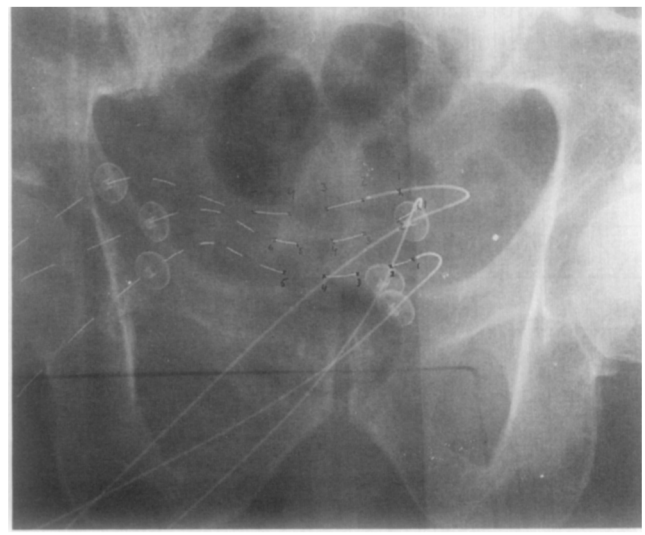

Fig. 1. Anterior–posterior photograph after insertion of catheters for IRT. Metal guidewires have been inserted at one end, whereas dummy sources with alternating pieces of lead and nylon with a length of 1 cm have been inserted from the other side.

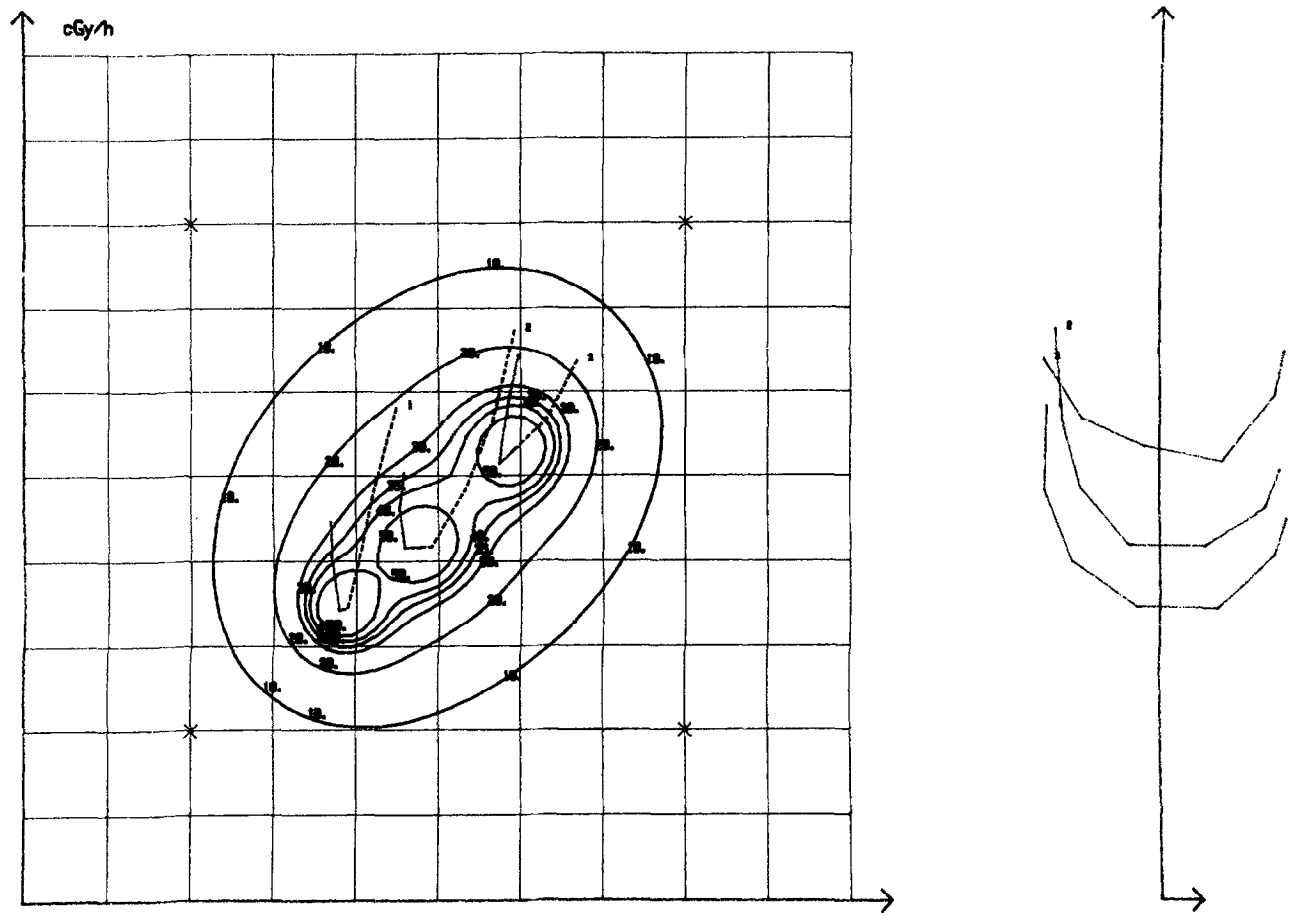

Fig. 2. Example of an isodose pattern in the central plane perpendicular to the iridium wires; the plane chosen and the position of the wires are shown on the right side of the figure.

different activities were used, in 1 the application time of one wire was increased and, finally, in 4 patients PDR was used.

In 62 patients, iridium wires were used: the mean dose rate was .58 Gy/h (range: .29–.96). The remaining four patients were treated with PDR, using a single iridium source: a fraction of 1 Gy was given every 3 h up to a total IRT dose of 30 Gy in three patients, whereas the fourth patient received 2 Gy fractions every 6 h up to 24 Gy.

Table 3. Sequence and doses of external beam (EBRT) and interstitial radiation (IRT)

Dose (Gy)			
EBRT	IRT	EBRT	No. of patients
10.5	60		1
10.5	30	30	1
10.5	37.2	40	1
40	30		54
40	35		4
40	24		1
40	32.5		1
42	30		1
40	26.4		1
40	16.6	12	1
			66

The application time in the one patient who received 60 Gy IRT was 110.2 h. The mean application time in the other 65 patients was 56.2 h (range 31.2–104).

IRT was started within 24 h after insertion of the catheters. Depending on the availability of the afterloading machine, the catheters were loaded with iridium remotely in 33 cases, whereas in the other half of the patients they were loaded manually.

After completion of the calculated application time the iridium was retracted, the catheters were removed and, subsequently, the patient was transported to the department at the hospital of the referring urologist for further postoperative care and recovery. The time of discharge depended on the policy of each department. The median hospitalization time was 17 days (range: 8 to 70 days).

Patients were seen regularly for follow-up thereafter, mostly during joint clinics, cystoscopies and urine cytology being performed routinely. Follow-up from the start of EBRT ranged from 5 to 78 months (median: 26 months).

Statistical methods

Data analysis has been primarily descriptive. A formal analysis of prognostic factors for bladder relapse was not

Table 4. Characteristics of the seven patients with a bladder relapse

Initial T-category	EBRT dose (gy)	Partial cystectomy (pT-category)	Lymphnode dissection (pN-category)	IRT dose (gy)	rT-category	Interval* (months)	Therapy	Distant metastases	Status
T2	40	n.p.	pN0	35	rT1	11	cystectomy (pT0)	no	alive (59m,NED)
T2	40	n.p.	n.p.	30	rT1	8	cystectomy (pTis)	subsequent	dead
T2	40	pT1	pN0	30	rT1	5	intravesical immunotherapy	subsequent	dead
T2	40	n.p.	pN0	24	rT1	6	none	concurrent	dead
T2	40	n.p.	n.p.	30	rT3a	14	systemic chemotherapy	concurrent	dead
T2	40	n.p.	pN0	30	rT3b	6	none	concurrent	dead
T2	40	pT0	pN0	35	rT4	11	ureter deviation	no	dead

n.p. = not performed; NED = no evidence of disease.
* Interval between start of treatment and diagnosis of bladder relapse.

feasible due to the small number of bladder relapses ($n = 7$) in this study. Survival curves were calculated by using the method of Kaplan and Meier.

RESULTS

Bladder relapse

In seven patients (11%, all T2 tumors) a bladder relapse developed. In five cases the tumor recurred at the original tumor site, in one a relapse was found elsewhere in the bladder, whereas in the remaining patient recurrent tumor was located in and outside the area of the primary. Four recurrent tumors invaded the lamina propria (rT1), in one tumor deep muscle infiltration was found (rT3a), one tumor invaded the perivesical fat (rT3b), and in one case the tumor was fixed to the pelvic wall (rT4). Cystectomy was performed in two patients with a rT1 relapse (pathological category pT0 and pTis); one of them remained disease free (59 months at the moment of data collection), the other died of distant metastases later on. The patient with rT4 disease underwent a palliative deviation of the ureters and died of local recurrence. One patient was treated with intravesical BCG instillations for a multiple rT1 process but died eventually of a fixed local recurrence and distant metastases. In the remaining three patients (rT1: $n = 1$; rT3a: $n = 1$; rT3b: $n = 1$), the bladder relapse was found together with distant disease; only one patient received systemic chemotherapy; all three patients died.

One patient had a TUR for a papillary transitional cell carcinoma, possibly with stroma infiltration, in the urethra; this is not considered as bladder relapse. Characteristics of the patients with a bladder relapse are given in Table 4.

The cumulative chance of remaining bladder relapse free at 5 years is 88% (Fig. 3).

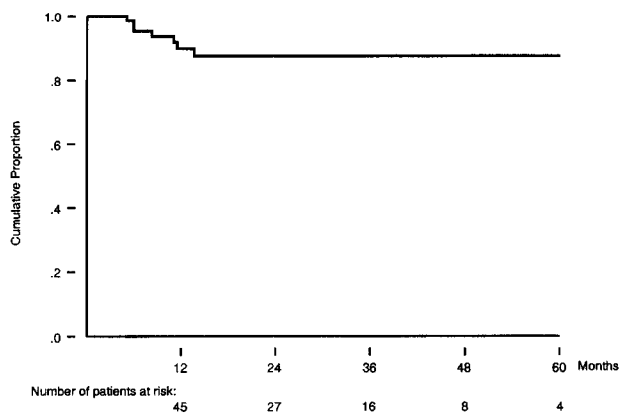

Fig. 3. Probability of remaining bladder relapse free, Kaplan-Meier curve.

Distant metastases

Metastases developed in 16 patients (24%). In five cases metastases occurred following ($n = 2$) or concomitant with ($n = 3$) a bladder relapse; the remaining 11 patients with distant metastases did not develop a bladder relapse. Ten patients did not receive any further antitumor therapy, in 4 patients systemic chemotherapy was given, 1 patient underwent palliative EBRT to penis and scrotum, and in 1 patient a palliative resection of a part of the small intestine was performed. All 16 patients eventually died.

The cumulative chance of remaining distant metastases free at 5 years is 66% (Fig. 4).

Survival

During the observation period 25 patients died. The cause of death was bladder cancer in 17 patients, whereas 3 patients died of a second primary (lung, stomach, prostate), and 5 of nonmalignant diseases.

The cumulative 5-year overall and bladder and distant relapse free survival rates are 48% and 69%, respectively (Fig. 5).

Complications

Acute toxicity. EBRT caused a raise in urination frequency to once every hour or more often (RTOG Grade 3)

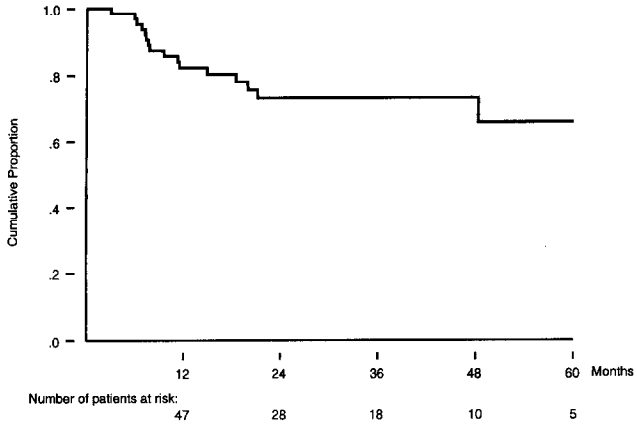

Fig. 4. Probability of remaining distant metastases free, Kaplan-Meier curve.

in only 9 patients (14%). No serious (i.e., RTOG Grade 3 or more) bowel/rectum or skin toxicity has been recorded.

In 30 cases (45%) no complications developed as a result of the operation or IRT. All acute toxicity of EBRT and surgery/IRT is given in Table 5.

A persisting vesicocutaneous fistula ("delayed wound healing" in Table 5) made surgical correction necessary in two patients and a wound toilet had to be performed in another one.

In two of the six patients with mental distress and/or confusion, IRT had to be terminated before the calculated application time had been completed, whereas in one patient a short interruption of IRT was necessary.

No patients experienced a lethal complication.

Late toxicity. RTOG Grade 3 bladder toxicity (frequency once every hour or more) developed in one patient (2%). No serious (i.e., RTOG Grade 3 or more) late bowel or rectum toxicity has been recorded.

During follow-up cystoscopies, necrosis was seen in the interstitially irradiated area of the bladder in nine patients (14%); this necrosis, however, caused symptoms (increased frequency and/or dysurea) in only two cases. The mean

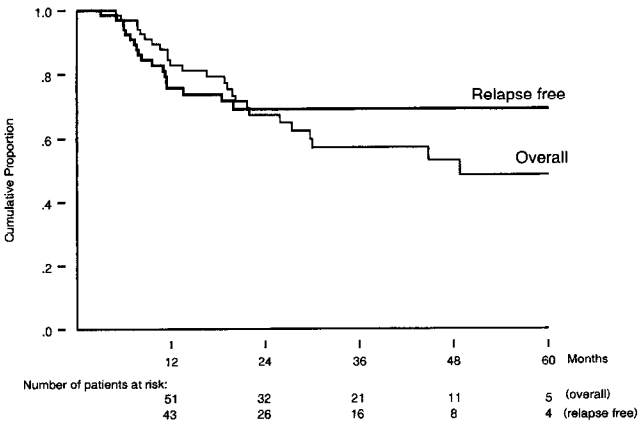

Fig. 5. Actuarial overall and bladder and distant relapse free survival, Kaplan-Meier curves.

Table 5. Acute toxicity

		RTOG	No. of patients	Percentage (%)
EBRT	Bladder	Grade 0	26	(39)
		Grade 1	26	(39)
		Grade 2	5	(8)
		Grade 3	9	(14)
	Rectum	Grade 0	18	(27)
		Grade 1	38	(58)
		Grade 2	10	(15)
	Skin	Grade 0	63	(95)
		Grade 1	2	(3)
		Grade 2	1	(2)
Surgery/IRT	Urinary infection		10	(15)
	Delayed wound healing		17	(26)
	Mental distress and/or confusion		6	(9)
	Cardiovascular		5	(8)
	Pulmonary		6	(9)
	Sepsis		1	(2)
	Subileus		1	(2)
	Other		10	(15)

period between IRT and the development of necrosis was 10 months (range 2–19).

In 13 patients (20%) incrustations in the IRT area of the bladder were noticed, causing complaints in one patient. Patients developing necrosis appeared to have a higher chance of incrustations than those in whom necrosis did not occur (44 vs. 14%, $p = 0.05$).

Finally, telangiectasia occurred in 15 patients (23%), causing intermittent hematuria (less than once a month) in only one patient.

Late bladder toxicity is summarized in Table 6.

DISCUSSION

Nowadays, IRT using the iridium afterloading technique aiming at organ preservation in bladder cancer patients, seems to be applied almost exclusively in Dutch and French centers (3, 31, 34, 37), although reports on two very small series have emerged from American centers as well (20, 40). Following the paper of Gros *et al.* (19) on the use of afterloading iridium wires instead of directly inserted radioactive material, French centers

Table 6. Late bladder toxicity

		No. of patients	Percentage (%)
Subjective*	Grade 0	61	92
	Grade 1	1	2
	Grade 2	3	5
	Grade 3	1	2
Objective	Necrosis	9	14
	Incrustations	13	20
	Telangiectasia	15	23

* RTOG grading.

adopted this technique soon afterwards (6, 14), whereas Dutch centers did not change their IRT technique until the last 10 years (3, 31, 53). In a nonrandomized study we did not detect a difference in the complication rate between a group of patients in whom caesium needles were used for IRT and a group of patients in whom the iridium afterloading technique was applied in the same period of time (53).

Compared to a not yet completely published series of 183 patients with muscle invasive bladder cancer, treated in our center by EBRT and radium or caesium needle implantation from 1981 until 1989 (54), the present series shows an improved bladder tumor control rate (88 vs. 70%) and similar survival rates.

Selection criteria appear to be quite similar in four recently published series on IRT using iridium in bladder cancer patients, in comparison to this report (3, 31, 34, 37). However, in the French centers a tumor biopsy was performed routinely prior to definitive therapy, and occasionally a tumor resection, i.e., almost all patients underwent a partial cystectomy or a resection of the tumor immediately before insertion of the catheters for IRT; in the series of Rozan *et al.*, apparently multiple mucosa biopsies were performed as well, to exclude patients with multiple tumors (34, 37). In the Dutch centers, a TUR of visible tumor was performed routinely without random biopsies; a partial cystectomy was only performed to facilitate IRT in some patients (8–24%) [present series, (3, 31)]. In our series, 6 out of 16 patients undergoing a partial cystectomy (37%) appeared to have a pT3 tumor, whereas their initial tumor was classified as T2, demonstrating the inaccuracy and risk of understaging in clinical staging of bladder cancer. Rozan *et al.* (37), as well as Pernot *et al.* (34) used a low dose of EBRT (11 Gy and 10.5 Gy, respectively) and a high dose of IRT (50 Gy), although Pernot *et al.* decreased the IRT dose to 30 Gy in case of large pT2 and pT3 tumors, adding postoperative EBRT. In the series of Battermann (3) and of Moonen *et al.* (31), 30 Gy EBRT and 40 Gy IRT were applied, whereas in the present series the majority of patients received 40 Gy EBRT and 30 Gy IRT.

In 18% of the patients with a pT2 or pT3a tumor (n = 92) in the series of Rozan *et al.* (37), a bladder relapse was observed. In the series of Battermann (3) (mainly T2 patients), 21% developed a bladder relapse, whereas in the series of Moonen *et al.* (31) in 21% of the T2 cases a bladder relapse occurred.

The probability of remaining bladder relapse free at 5 years in pT2 tumors in the series of Pernot *et al.* (34) was 64%. The observed bladder relapse rate (11%) and the cumulative chance of remaining bladder relapse free at 5 years (88%) in our series compare favorably to these data. The bladder was preserved in 98% of the surviving patients in our series, whereas in 84% of the patients who died during the observation period bladder functioning was retained.

Half the percentage of the bladder relapses in the series of Moonen *et al.* (31) and 71% of the bladder relapses in our series occurred at the original tumor site, whereas tumor recurrence was actually local in only 29% of the relapses in the pT2 and pT3 cases of Rozan *et al.* (37). A possible explanation for this difference might be that by using a higher dose of EBRT in the Dutch centers a more homogeneous dose is applied to the whole bladder mucosa, thereby possibly killing (pre)malignant cells outside the tumor area. One would expect that by excluding patients with multiple tumors detected by random biopsies, as reported by Rozan *et al.* (37), the number of relapses outside the original tumor area will be low. However, according to the abovementioned percentages with respect to site of bladder relapses, this seems not to be the case.

In our series, three of the seven patients with a bladder relapse (43%) had concurrent distant metastases. Moonen *et al.* (31) report concurrent metastases in four of the six patients with a bladder relapse (66%), whereas in the series of Rozan *et al.* (37) this is 28%. In both Dutch series, bladder relapses developed in patients with T2 tumors only, whereas in the French series 42% of the bladder relapses occurred in patients treated for a pT1 tumor, which might explain the difference in the development of concurrent metastases.

Three of the 42 patients (7%) in our series who underwent a lymphnode dissection appeared to have nodal metastases; Rozan *et al.* (37) report 2.5% node metastases, whereas Pernot *et al.* (*34*) discovered nodal metastases in 25% of the patients with "larger and more infiltrating tumors". Unless the treatment plan will be changed, or adjuvant systemic chemotherapy will be offered in case of positive nodes, a lymphadenectomy does not seem to be warranted in patients with bladder cancer selected for IRT.

Although Gros *et al.* mentioned the possibility of optimization of the dose distribution by "playing" with the activity or the application time of different iridium wires within one implant as early as 1969 (19), so far this has not been reported in any other article on IRT in bladder cancer. We optimized the dose distribution in 11 patients by using different activities of iridium, different applications times, or by applying PDR; however, we were not able to prove a positive effect.

Distant metastases developed in 22% of our patients, whereas 15% (mainly T2 cases) and 18% (T2 cases only) were reported by Battermann (3) and by Moonen *et al.* (31), respectively. Due to a relatively large number of intercurrent deaths the actuarial 5-year overall survival was only 48% in our patients. The actuarial 5-year bladder and distant relapse free survival was 69%, in accordance with the data from the French centers [Pernot *et al.*: pT2 cases: 76%; pT3 cases: 72% (34); Rozan *et al.*: pT2 cases: 80.9%; pT3 cases: 62.2% (37)].

Because different definitions are used, a comparison of acute and late toxicity in the different papers is hardly

possible. In our opinion, the three patients in our series in whom a second operation was necessary due to wound healing problems represent the most serious toxicity of surgery followed by IRT. Lethal complications were not encountered in Rotterdam, although three other article report an occurrence of 2–3% (3, 34, 37).

Late complications such as ulceration/necrosis and incrustations/bladder stone formation are not uncommon, but asymptomatic and temporary in the majority of cases [present series, (3, 31, 34)].

We were not able to detect any influence of IRT dose, dose rate, application time, and length of iridium wires on the development of complications. Pernot *et al.* (34) report that serious toxicity in 5 patients was related to dose rate (.62 Gy/h), surface area, spacing of the wires and start of IRT on the day following the operation. French centers advise loading of the catheters a week after surgery (34, 37). In our experience, a mean dose rate of .58 Gy/h and start of IRT within 24 h after surgery are not related to serious toxicity, although one should keep in mind that the IRT dose applied in our center is generally lower than that reported in the French series.

Because randomized studies have not been performed and because IRT in bladder cancer is applied in a selected group of patients, a proper comparison with the results of other treatment modalities is not possible.

In many centers, patients with muscle invasive bladder cancer undergo a radical cystectomy; as a result, the possibility of natural voiding is sacrificed. Recent series (18, 29, 39, 42, 56) reported 5-year overall survival rates varying from 23–82% after radical cystectomy. Radical EBRT offers the possibility of preserving the bladder, but local relapse rates of 35–61 and 48% to >70% have been reported for T2 and T3 tumors, respectively, whereas the overall 5-year survival varies from 10–64% (4, 11, 13, 16, 17, 28, 36).

The alternating or concomitant application of systemic chemotherapy and radical EBRT has been reported to result in high complete response rates with bladder preservation in 38–58% of the patients (9, 33).

Finally, in many studies neoadjuvant chemotherapy and EBRT with concomitant chemotherapy have been used to select patients for bladder preservation, which is eventually achieved in up to 70% of the cases (1, 15, 25, 41, 50).

It remains unclear which patients should be selected for any of the latter two therapies mentioned, with the possibility of bladder preservation, whereas selection criteria for IRT are well defined.

CONCLUSION

Interstitial radiation preceded by transurethral resection and external beam radiotherapy in a selected group of patients with muscle invasive bladder cancer yields an excellent bladder tumor control rate, with a very high probability of bladder preservation. Survival is mainly dependent on the development of distant metastases. Serious acute and late toxicity is rare. A close cooperation between urologist and radiation oncologist is an essential condition for achieving these results, as well as the availability of modern brachytherapy facilities.

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