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Intra-operative electron radiotherapy as a conservative treatment for infiltrating bladder cancer

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Abstract

The intent of this feasibility study was to evaluate the use of intra-operative electron radiotherapy (IOERT), after transurethral resection (TUR), combined with external beam radiation with concurrent chemotherapy for the conservative treatment of infiltrating bladder cancer. From November 1988 to June 1998, 27 patients with histologically proven non-metastatic infiltrating bladder cancer were included in this protocol. The treatment consisted of: TUR, external beam irradiation (×18 MV:48 Grays (Gy)/24 fractions/5 weeks), with concurrent chemotherapy (cisplatin 30 mg/day for 3 days–two cycles during irradiation), followed by control cystoscopy and cystotomy with IOERT (e 9 MeV:15 Gy). 14 patients received two cycles of neoadjuvant methotrexate, vinblastine and cisplatin (MVC) and folinic acid chemotherapy. Patients were evaluated for toxicity, local control and survival. The 5-year overall and cystectomy-free survival rates were 53.3% ±11.1% and 48.1%±11.4%, respectively. 4 patients developed infiltrating intravesicular recurrence (3 were treated by salvage cystectomy), and an additional patient developed a superficial recurrence. 2 patients subsequently developed regional recurrence in pelvic nodes and 10 patients were found to have distant metastases. The protocol was found to be feasible and associated with acceptable toxicity. Early and late toxicities consisted of 3 cases of bladder mucosal necrosis or ureteral stenosis which resolved with medical management. These preliminary results indicate that IOERT combined with TUR and neoadjuvant external beam radiation with concurrent chemotherapy is feasible. It could be considered as an alternative therapy for infiltrating carcinoma of the bladder, especially in patients unfit for radical surgery, and is well adapted to treat lesions of the fixed portion of the bladder.

Keywords: Bladder cancer; Intraoperative electron radiotherapy; Bladder preservation; Chemotherapy

1. Introduction

Carcinoma of the urinary bladder cancer is responsible for 4000 deaths every year in France. The median age at presentation is 65 years and the risk of developing bladder cancer is increased in smokers and patients with co-morbid illnesses, especially respiratory and cardiovascular disease [1]. The 5-year overall survival rate is approximately 50% which decreases with increasing depth of tumour infiltration into the bladder musculature and surrounding structures. Prognosis depends not only on the extent of local tumour but also on the development of distant metastases (20% for stage T2, 80% for stage T3b) [2].

In France, radical cystectomy is the standard treatment for invasive carcinoma of the bladder. New strategies, however, are currently being developed in an attempt to utilise bladder conservation as a treatment alternative while continuing to provide acceptable local control, decreasing treatment-related toxicity and improving quality of life. Conservative treatment of bladder cancer with concurrent external beam and intra-operative electron radiotherapy (IOERT) have been used with some success in Japan since 1960, [3,4] and in the USA since 1976 [5,6]. Similar techniques have been under investigation in France since 1984 [7,8].

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The rationale behind the use of IOERT as a component of the treatment regimen is to escalate the dose delivered to the tumour bed while limiting the dose delivered to the uninvolved portion of the bladder and surrounding dose-limiting normal tissues [9]. This is achieved during cystotomy when the tumour bed is adequately exposed permitting a localised delivery of a high irradiation dose directly to the tumour in a single fraction (10–18 Gy by electrons) [10].

We report the results of combining external beam irradiation with concomitant chemotherapy and intraoperative radiotherapy delivered after transurethral resection of the tumour. The objective of this pilot study was to determine if bladder conserving therapy utilising such a protocol was feasible, associated with acceptable toxicities and provided adequate local control and preservation of bladder function.

2. Patients and materials

2.1. Patients

From November 1988 to June 1998, 27 patients referred by the urologists with histologically proven infiltrating urothelial bladder carcinoma tumours, without distant metastases detectable by abdominopelvic sonography or bone scan, were included prospectively in this protocol. 12 patients included in this study were considered ineligible for radical cystectomy due to comorbid illnesses. 7 operable patients refused radical surgery. One additional patient included in this study was found to have pelvic lymphadenopathy by computer tomography (CT) scan at the time of diagnosis and was ineligible for surgery. In 7 cases, although a radical cystectomy was possible it was decided jointly by the urologist and radiation oncologist to treat the patient after informed consent with this conservative approach. The initial histological diagnosis was made at cystoscopy. All tumours were found to be less than 6 cm in maximum dimension (2–5 cm). Initial surgical celioscopic lymph node exploration was performed at the time of diagnosis in 6 patients, while 14 patients had this exploration after the concomitant chemoradiation, at the time of IOERT and 7 patients did not undergo any lymph node dissection. Nodal involvement was proven histologically in 4 patients (3 pN1 and 1 pN2) by celioscopic lymphadenectomy at the time of transuretheral resection, including 1 patient presenting with a pelvic lymphadenopathy by CT. No positive node was discovered at the time of IOERT. In all cases, a full node dissection of the external iliac and obturator nodes was performed.

The median age of patients at the time of treatment was 63 years (range: 43–80). The clinical and pathological characteristics of these patients are presented in Table 1.

2.2. Treatment

Transurethral resection was used initially as a diagnostic and therapeutic procedure. Initial transurethral resection was considered complete in 12 patients (44%). 14 patients (52%) in the initial period received neoadjuvant chemotherapy, before external beam irradiation, consisting of two cycles of methotrexate 30 mg/m^2 days 1 and 8, vinblastine 4 mg/m^2 days 1 and 8, cisplatin 100 mg/m^2 day 2, and folinic acid 15 mg 4 times days 2 and

Table 1
Anatomical and clinical criteria ($n=27$)

	n (%)
Age (years)	
Median (range)	63 (43–80)
<60	10 (37)
60–70	11 (41)
70–79	5 (19)
80	1 (4)
Sex	
Male	23 (85)
Female	4 (15)
Rectal examination	
Normal	19 (70)
Palpable tumour	8 (30)
IVP	
Normal	13 (48)
Ureteral dilatation	8 (30)
Unknown	6 (22)
Histology	
Urothelial carcinoma	25 (93)
Epidermoid carcinoma	2 (7)
Site	
Lateral wall	12 (44)
Anterior wall	2 (7)
Lateral wall + Trigone	13 (49)
TNM classification	
T2	22 (81)
T3	5 (19)
N0	26 (96)
N1	1 (4)
pN0	15 (55)
pN1	3 (11)
pN2	1 (4)
Histological grade	
I	0
II	2 (7)
III	19 (70)
Unknown	6 (22)
Distance from ureteral orifice	
$\leqslant 3$ cm	24 (89)
>3 cm	2 (7)
Unknown	1 (4)
Recurrence after TUR	
Yes	11 (41)
No	16 (59)

TUR, transurethral resection; IVP, intravenous pyelography.

9 every 21 days (MVC). 13 patients (48%) did not receive this chemotherapy due to co-morbid illness and poor general medical condition. External beam irradiation, using 18 MV photons and a 4-field technique consisted of 48 Gy in 24 fractions over 5 weeks being delivered to the isocentre. Treatment planning was done using a simulator with contrast medium and folley catheter to localise the bladder. The target volume included the gross tumour, the whole bladder and the external iliac nodes to the level of the mid sacro iliac point. In 4 cases with positive nodes, internal iliac nodes were included to the level of the L5/S1 disc. Average dimension of fields was anterior posterior.posterior anterior (AP.PA): 13×12 cm and lateral 12×11 cm. The prescribed and specified dose was given to the ICRU point at the isocentre of the field. All patients received an additional two cycles of cisplatin 30 mg/m^2 continuous perfusion from day 1 to day 3 during the first and fifth weeks of radiotherapy. 3 patients (11%) had a dose reduction or delay in chemotherapy; 2 secondary to renal toxicity and 1 due to haematological complications.

Cystoscopy was performed 4 weeks after the completion of external beam radiation therapy to assess tumour response. If there was no clinical evidence of persistent disease no elective biopsy was performed. Total cystectomy was planned to be performed in case of tumour progression.

Approximately 6 weeks after the completion of external beam irradiation (range: 4 to 11 weeks), an additional dose was delivered intra-operatively at the time of cystotomy. The tumour bed was exposed during surgery and a single dose of 15 Gy with 9 MeV electrons was delivered through a cone of 6 cm in external diameter to the tumour bed. Positioning of the cone was easily and accurately performed in all patients as a residual small induration or a whitish scar in the area of previous disease allowed the exact location of the primary tumour. IOERT preceded external beam irradiation in 3 cases (11%), so that patients who were suspicious for lymph node involvement could be evaluated further prior to treatment.

Lymph node status was re-evaluated at the time of surgery. 4 patients (15%) were found to have histologically proven lymph node involvement including the patient with radiological evidence of adenopathy prior to therapy, despite the resolution of adenopathy by CT after chemotherapy.

2.3. Evaluation of response and toxicity

Evaluation of response to treatment was performed by cystoscopy every 6 months after the completion of therapy. The median time to follow-up for all patients was 46 months with 5 patients followed for longer than 5 years. No patients were lost to follow-up. A complete clinical response was defined as the absence of any residual macroscopic tumour at cystoscopy, a partial clinical response as the reduction of the macroscopic tumour volume by more than 50%, and the objective clinical response included both complete and partial responses. Urine cytology was evaluated during treatment and every 6 months at the time of follow-up. Biopsy was reserved for clinical evidence of suspicious lesions in the bladder. Systemic work-up for distant metastases using appropriate diagnostic techniques was performed only if patients displayed clinical manifestations.

Analysis of toxicities was performed and recorded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) scoring system [11]. Bladder function and reserve were evaluated by patient survey at the time of follow-up.

2.4. Statistical analysis

The overall survival, disease-free and cystectomy-free survival rates were calculated for the time interval between the start of treatment and date of death, or date of last follow-up during or prior to 1 June 1998. Statistical analyses were performed using EPI, INFO and SPSS. Overall, disease-free and cystectomy-free survivals with standard errors were calculated using the Kaplan–Meier method and comparisons of survival were made by the log rank test [12]. For disease-free survival, events taken into account were any cancer failure or death for any reason.

3. Results

3.1. Response

Out of the 27 patients, 24 (89%) were treated with first-line external beam irradiation (EBRT) with concurrent chemotherapy. At the time of control cystoscopy 4 weeks after completion of EBRT before surgery, all of these 24 patients (100%) were found to have an objective clinical response, of which 18 patients (75%) had a complete clinical response. No patient demonstrated disease progression during treatment. Three months after IOERT all the patients had a complete response in their bladder at control cystoscopy.

3.2. Survival

Overall and cystectomy-free survival curves are displayed in Fig. 1 and Table 2. The 5-year overall survival rate was 53.3% (standard error of the mean (SEM) = 11.1%), while the 5-year cystectomy-free survival rate was 48.1% (SEM = 11.4%). The 5-year disease-free survival was 46.2% (SEM = 11.3%) (data not shown). 10 patients (37%) developed metastases (9 patients within

Table 2
5-year overall survival and cystectomy-free survival

	Overall survival			Cystectomy-free survival		
	Survival	SEM	*n* patients[a]	Survival	SEM	*n* patients[a]
At 5 years	53.3%	11.1	5	48.1%	11.4	5

SEM, standard error of the mean.
[a] Number of patients at risk at 5 years.

the 24 months following treatment and 1 patient after 33 months) (Table 3). Sites of metastases included: bone (4 patients), bone and liver (2 patients), bone, liver and lung (1 patient) brain (1 patient) and lung (2 patients). All patients who developed distant metastases were dead of disease within 3 years following treatment. Of the 4 patients who presented with histologically proven lymphadenopathy, 3 are dead of disease, while the fourth is still surviving with pulmonary metastases.

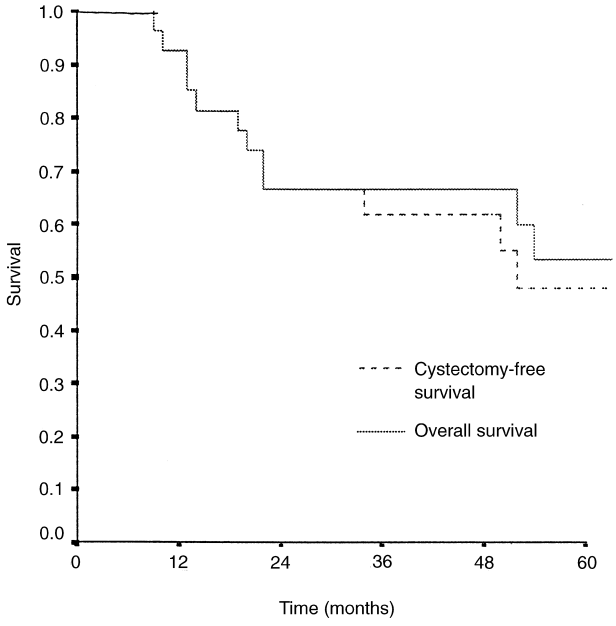

Fig. 1. Overall survival and cystectomy-free survival.

3.3. Local and regional control

4 patients developed infiltrating intravesicular recurrence. One patient recurred at 36 months after treatment and died postoperatively after salvage radical cystectomy. Another patient recurred 4 months after treatment, was treated palliatively and died 6 months after recurrence from local regional complications. The

Table 3
Patients' characteristics, treatment and results[a]

n	Date TT	Age	Sex	Histology	cT	cN	pN	IOERT First	Neoadjuvant chemotherapy	Bladder	Relapse Regional node	Metastases	Necrosis G3	Death	Date of death
1	1988	63	M	Uroth	2	0	0			+		+		+	1993
2	1989	50	M	Uroth	2	0	0		+			+		+	1991
3	1990	68	M	Uroth	3	0	0		+						Alive
4	1990	54	M	Uroth	2	0	×	+							Alive
5	1990	78	M	Uroth	2	0	0		+			+		+	1991
6	1991	76	M	Uroth	2	0	×		+		+				1993
7	1992	80	M	Uroth	3	0	1		+	+				+	1993
8	1992	56	M	Uroth	2	0	0		+				+		Alive
9	1992	68	M	Uroth	2	0	×		+						Alive
10	1992	48	M	Uroth	2	0	0		+	+					Alive
11	1992	72	F	Uroth	2	0	0	+	+			+		+	1993
12	1991	62	M	Uroth	2	0	0		+			+		+	1993
13	1993	61	M	Uroth	2	0	×		+			+	+	+	1997
14	1993	49	M	Uroth	2	0	0	+	+						Alive
15	1993	67	M	Uroth	2	0	0		+	+ (IS)		+		+	1998
16	1993	61	F	Uroth	2	0	0								Alive
17	1993	75	M	Uroth	3	0	1								Alive
18	1993	43	M	Uroth	2	1	2					+		+	1994
19	1993	57	M	Uroth	2	0	×						+		Alive
20	1993	57	M	SCC	3	0	0								Alive
21	1993	76	F	Uroth	2	0	0								Alive
22	1993	52	M	Uroth	2	0	0			+		+		+	1995
23	1994	50	M	Uroth	2	0	×								Alive
24	1994	63	M	SCC	2	0									Alive
25	1994	65	M	Uroth	2	0	×				+			+	1996
26	1993	67	F	Uroth	3	0	1					+		+	1994
27	1995	64	M	Uroth	2	0	0								

M, male; F, female; Uroth, urothelial carcinoma; SCC, squamous cell carcinoma; pN, pathological stage node; IS, carcinoma *in situ*; TT, treatment; cT, clinical stage tumour; cN, clinical stage node; IOERT, intra-operative electron radiotherapy.
[a] 27 patients treated with IOERT between 1988 and 1995.

third patient recurred 12 months after treatment and he died 1 year after salvage cystectomy.

The final patient recurred at 71 months, and was treated with salvage cystectomy.

One patient presented with superficial vesicular recurrence 30 months after treatment and was successfully resected, but died from metastatic disease without intravesicular recurrence 1 year later.

2 patients experienced regional recurrences, presenting with iliac lymphadenopathy and no evidence of intravesicular recurrence at 3 and 19 months, respectively, after the completion of therapy. They both died from complications of regional recurrence without developing metastases. The remaining 20 patients did not show any clinical evidence of local regional recurrence.

3.4. Toxicity

There was no treatment-related mortality and all patients received the full uninterrupted course of radiotherapy. Chemotherapy was interrupted and the dose was reduced in 3 patients (11%) secondary to haematological or renal toxicity.

Acute complications were frequent but moderate, 12 patients (44%) experienced grade 1 and 2 gastrointestinal complications during concomitant chemoradiation. 7 patients (26%) developed grade 1 and 2 urinary complications. Treatment-related radiation cystitis was noted in 5 patients (19%) and was treated medically in 2 patients. 2 additional patients (7%) suffered renal complications (transient increase in creatinine) which necessitated the interruption of chemotherapy. One patient (4%) experienced neutropenia grade 3 and treatment was interrupted. There were 3 surgical complications which included lymphoedema, occurrence of a lymphocele and lymphorrhoea.

Moderate late complications occurred in 2 patients (7%). One developed asymptomatic retroperitoneal fibrosis and the other suffered from prepubic and left lower limb oedema following development of a lymphocele, resolved by surgical intervention.

3 (11%) grade 3 late complications were noted. In 1 patient, bladder wall and pubic necrosis developed following the treatment of an anterior tumour for which IOERT had involved the pubic bone. This necrosis required medical treatment only. Another patient developed vesicular necrosis resulting in dilation of the proximal urinary tract 2 years after the completion of treatment. The necrosis was limited to the intra-operative radiation field. This patient was successfully treated medically. The third patient developed ureteral stenosis and hydronephrosis 1 year after the completion of therapy. This patient was also treated with nephrostomy and insertion of a double J catheter. The 3 patients who developed grade 3 late complications received an intra-operative dose of 15 Gy, using 9 MeV electrons for 2 patients and 12 MeV for the third.

No cases of contracted bladder were reported. All patients maintained satisfactory reserve capacity and normal bladder function, and they all reported good bladder function throughout follow-up. At 5 years, 5 patients are alive with a normally functioning bladder without any severe complications.

4. Discussion

In France, radical cystectomy remains the standard treatment of choice for infiltrating bladder cancer. Radical cystectomy results in a 5-year overall survival rate of 50%, however, the morbidity and the psychological impact on the patient remains problematic [13,14]. A retrospective study of 130 patients treated with radical cystectomy demonstrated a 5-year survival rate of 53% and operative morbidity and mortality rates of 15% and 6%, respectively. Those results are similar to major series of cystectomy in the literature [2,15,16].

In some countries, external beam radiotherapy alone is considered first-line treatment for invasive bladder cancer, with salvage cystectomy reserved for local failure. With such an approach, 5-year overall survival is close to 35%, and local control, with preservation of good bladder function, is obtained in 50% of patients [17–20].

In 1982, Bloom and colleagues published the results of a randomised trial, comparing total cystectomy and exclusive radiotherapy. They treated 189 patients in the period between 1966 and 1975. The results of total cystectomy were better in patients under 70 years of age, while in patients above 70 years, the results of both groups were identical [21].

The rationale behind the use of IOERT, in addition to external beam radiotherapy, is to escalate the dose to the tumour bed, while avoiding the surrounding tissues to obtain better local control, resulting in a preserved acceptable bladder function. This technique was originally proposed by Shipley and colleagues [6] and our approach was directly inspired by his proposal. The analysis in this pilot study of 27 patients shows a 15% (4/27) rate of local failure. With external beam irradiation alone, 30% local failure rate is reported [19,22]. Selection bias may exist as the patients included in our series were deemed inoperable and referred for primary non-surgical therapy by surgeons prior to inclusion in this study. Hence no strict comparison to other series can be made and it is difficult to know what the specific effect of IOERT is.

The dose of IOERT used in this study was 15 Gy and we observed 3 cases of transient bladder necrosis. Based on this experience, we are currently recommending an IOERT dose of 12 Gy, where complete gross response to TUR and external beam radiation (with or without

chemotherapy) is achieved and IOERT is directed towards subclinical disease. An alternative to IOERT to escalate the dose is the use of carefully planned conformal radiotherapy. It has the advantage over IOERT of delivering a fractionated irradiation which is less toxic than single doses. However, it is difficult to clearly see and contour the target volume of a bladder tumour after TUR and IOERT with an opened bladder has the merit of a very precise delivery of the radiation dose to the tumour (or tumour bed) only with a perfect protection of the surrounding normal bladder.

Two other institutions have also reported results utilising IOERT in the treatment of invasive bladder cancer. Matsumoto and colleagues reported the results of IOERT in 116 patients, 94 of whom were Ta, T1 or T2. The 5-year overall survival in this series was 88%, with a 5-year local recurrence rate of 19% [23]. In another series of 34 patients, Calvo and associates utilised a different approach where IOERT was not used to preserve the bladder, but to increase the dose to the bladder before radical cystectomy. Patients underwent two surgical procedures. The first, a laparotomy, was performed to deliver the dose of IOERT, and bilateral pelvic lymphadenectomy and ileo-ureteral diversion was performed at this time. The second, was to perform cystectomy after external beam radiotherapy. Complete pathological response was found in 68% of the cystectomy specimens. In this series, only 1 patient (3%) developed a pelvic recurrence at the edge of the external beam radiation field. These data provide evidence that IOERT is effective in enhancing local control in areas at risk for local recurrence [17].

Another technique which has been utilised to further improve local control in bladder conserving regimens, is the use of interstitial brachytherapy to deliver an escalated dose to the tumour bed [24–26]. The rationale behind this technique is the same as for IOERT; i.e. increasing the dose directly to the tumour and avoiding the surrounding normal structures. Thus, the therapeutic ratio is enhanced by increasing the probability of local tumour control, while decreasing the risk of treatment-related complications. Interstitial brachytherapy is accomplished by placing plastic catheters in the tumour bed at the time of surgery. These catheters are then loaded with 192-Iridium wires for a prescribed time necessary to achieve a dose of 20–50 Gy. Interstitial brachytherapy has been used with or without external irradiation (± chemotherapy) for bladder conservation. One series reported a 66.8% 5-year overall survival for 205 patients treated with interstitial brachytherapy as a part of the treatment regimen [27]. Currently in Lyon, this technique is reserved mainly for tumours of the dome of the urinary bladder where it is difficult to deliver IOERT [28,29].

Chemotherapy is routinely used for metastatic disease. The complete response rate to this type of combined modality regimen utilising MVC or methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) is reported to be 40% from phase II trials [30]. Chemotherapy has also been used adjuvantly to surgery without proven survival benefit [2].

Chemotherapy used neoadjuvantly, before cystectomy or radiotherapy, such as two cycles of MVC, was not shown to increase the rate of complete response, disease-free survival and overall survival [31].

The benefit of using concomitant radiochemotherapy has been advocated by several reports from different centres. Concomitant chemotherapy in the form of cisplatin 60–100 mg/m^2 over 3–5 days, during the first and the fifth weeks of treatment when given during external beam irradiation, has resulted in a complete response of the bladder tumour of between 66 and 78%. However, although there was an improvement in local control, it is difficult to demonstrate its impact on overall survival [22,32–34].

Based on the data provided from this feasibility study and a review of results published in the literature, acceptable local control and toxicity can be achieved using IOERT as a component of treatment for invasive bladder cancer. Despite adequate control of the disease in the pelvis, the development of metastases remains problematic and patients often succumb to distant disease.

Infiltrating bladder cancer remains a disease of poor prognosis. Treatment with radical cystectomy carries a high treatment-related morbidity and is sometimes not suitable for elderly patients and patients with co-morbid illnesses. The present study shows that it is possible to use IOERT to boost the tumour bed after concurrent chemoradiation for infiltrating bladder cancer with an acceptable rate of toxicity. Although radical cystectomy remains in France, as in many countries, the standard treatment of invasive bladder cancer such a conservative approach could be considered as a reasonable alternative for solitary tumours of the fixed part of the bladder, 5 cm or less in maximum diameter in patients unfit for total cystectomy.

Metastatic progression remains a significant problem limiting survival in these patients, especially in the presence of pelvic or para-aortic adenopathy.

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