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ORIGINAL ARTICLE

Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer

Emmanuelle Fabiano[a], Catherine Durdux[a], Bertrand Dufour[b], Arnaud Mejean[c], Nicolas Thiounn[c], Yves Chrétien[c], Jean-Emmanuel Bibault[a], Philippe Giraud[a], Sarah Kreps[a], Antoine Smulevici[a], Safia Maraadji[a] and Martin Housset[a]

[a]Department of Radiation Oncology, European Hospital Georges Pompidou, University of Paris Descartes, Paris, France; [b]Department of Urology, Necker Hospital, University of Paris Descartes, Paris, France; [c]Department of Urology, European Hospital Georges Pompidou, University of Paris Descartes, Paris, France

ABSTRACT

Purpose: To evaluate trimodal conservative treatment as an alternative to radical surgery for urothelial muscle-invasive bladder cancer (MIBC).

Patients and methods: This retrospective study reported the carcinologic and functional results of patients (pts) presenting a cT2/T3 *N*0M0 operable MIBC and fit for surgery, treated by a conservative strategy. Treatment consisted of a transurethral resection (TURB) followed by concomitant bi-fractionated split-course radiochemotherapy (RCT) with 5FU-Cisplatine. A control cystoscopy was performed six weeks after the induction RCT (eq45Gy) with systematic biopsies. Patients with complete histologic response achieved RCT protocol. Salvage surgery was proposed to pts with persistent tumor.

Results: 313 pts (83% cT2 and 17% cT3) treated between 1988 and 2013 were included, with a median follow-up of 59 months and 67-year mean age. After the induction RCT, the histologic response rate was 83%. After five years, overall, disease-free, and functional bladder-intact survival rates were respectively 69%, 61%, and 69%, significantly better for pts in complete response after induction RCT. Late urinary and digestive toxicities were limited, with respective rates of 4% and 1.5% of grade 3 toxicity.

Conclusion: Trimodal strategy with RCT after TURB showed interesting functional and oncologic results and should be considered as an alternative to surgery in well-selected pts.

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KEYWORDS
Bladder cancer; trimodal treatment; organ sparing treatment; radiotherapy; outcome assessment

Background

Bladder cancer is the 11th most commonly diagnosed cancer worldwide. For localized muscle-invasive bladder (MIBC), treatment includes induction chemotherapy, followed by radical cystectomy [1,2]. Advances in the surgical technique and perioperative care, significantly reduced complication rates. On the other hand, orthotopic neobladder may have a positive impact on quality of life but has the potential of increasing short and long-term complication rates, compared to standard urinary diversion [3,4]. However, Hautmann's study shows that among 923 patients (pts) having had an orthotopic neobladder, 40% had late complications [5]. More than one-third of pts develop metastasis within 3 years after surgery, particularly pts with pT3 stages. In this context, alternative conservative strategies have been developed during the last decade, following approaches similar to the anal canal or laryngeal cancer treatments.

The usual conservative approach in MIBC is a trimodal treatment (TMT). It consists in a transurethral resection of the bladder tumor (TURBT) as complete as possible, followed by concomitant radiochemotherapy. Response to radiochemotherapy is then assessed by cystoscopy with large biopsies. Planned surgery is proposed to non-responder pts and additional chemoradiotherapy with careful regular endoscopic examination is performed in responders [6].

Except for the incomplete selective bladder preservation against radical excision (SPARE) trial, there is no large and meaningful randomized trial comparing radical cystectomy and TMT [7]. Several single-institution series and prospective trials conducted by radiation therapy oncology group (RTOG) have shown that the conservative approach can achieve high rates of complete histologic response, bladder conservation in many pts, and survival rates similar to recent surgery series in well-selected pts [8–10]. In these series, protocols were heterogeneous, even within a single department, with or without induction or adjuvant chemotherapy.

In 1988, our institution started a prospective study combining TURBT and chemoradiotherapy, with fluorouracil (5-FU)/cisplatin plus concomitant bifractionated split-course radiation therapy, followed by cystectomy or additional chemoradiotherapy in pts with muscle invading primary transitional-cell carcinoma of the bladder and fit for surgery [11]. Herein, we report long-term results of a larger series of 313

CONTACT Emmanuelle Fabiano emmanuelle.fabiano@aphp.fr Department of Radiation Oncology, European Hospital Georges Pompidou, University of Paris-Descartes, 20 rue Leblanc, 75015, Paris, France

pts fit for surgery treated according to this protocol with a 59-month minimum follow-up period.

Material and methods

Patients

From February 1988 to December 2013, all pts with a clinical-stage T2-T3N0M0, histologically proven, urothelial carcinoma of the bladder were included in this study. Patients with other histology than urothelial carcinoma were excluded from the study. All pts had unifocal and invasive, operable c*N*0 tumors and were fit for surgery. The decision to treat with TMT relied on the patient's choice after the presentation of the different therapeutic options.

For analysis, tumor staging was assessed according to the 7th AJCC classification (2009) after clinical examination and thoracoabdominopelvic CT scan. Exploration of the superior urinary tract was done with uroscan or intravenous pyelography if the renal function was normal. Bone scintigraphy could be performed in case of hypercalcemia or symptoms of possible bone metastasis.

Data for this study was declared to the French National Data Protection Comity. Patients' consent was waived in accordance with the CNIL (Commission Nationale de l'Informatique et des Libertés) decision given on 2 February 2016 for all data collected on pts' routine care treated in our institution (CNIL 1922081).

Treatment

All pts had initial TURBT for diagnostic and therapeutic purposes. The objective was to achieve complete macroscopic resection for cT2 tumors before beginning chemoradiotherapy. If complete removal of tumor was not achieved or dubious after the first TURBT, a second one could be performed. For cT3 tumors, the objective of the TURB was to obtain a maximal reduction of the tumor volume without risking bladder perforation.

In all pts, radiotherapy was performed by 4 to 25 MV photons of a linear accelerator, with a 2D-technique before 1996 and 3D conformational radiotherapy with planning CT scan after 1996. The whole bladder and pelvic bilateral external, internal, and obturator lymph nodes were included in a four-field box technique. A dose of 24 Gy was delivered in eight fractions over 17 d, according to a modified bi-fractionated split-course schedule. All fields were treated twice on days 1, 3, 15, and 17. Each fraction delivered 3 Gy on the target volume. The interval between the two daily fractions was at least 6 h.

All pts received a combination of intravenous 5-FU/cisplatin concomitantly with radiation. Cisplatin (15 mg/m^2/d) and 5-FU (400 mg/m^2/d) were administered as a short infusion over 2 h on days 1, 2, 3, 15, 16, and 17. On days 1, 3, 15, and 17, chemotherapy infusion was begun 2 h before irradiation. The blood count and serum electrolytes levels, as well as creatinine levels, were checked at least weekly. Variations in this protocol could be decided according to clinical and biological chemotherapy tolerance. In the case of cisplatin contraindication, especially due to renal impairment as evidenced by poor creatinine secretion, carboplatin AUC 2 could be used. Patients with cardiovascular diseases had a cardiology consultation before 5-FU administration.

A control cystoscopy with deep biopsies was systematically performed 6 weeks after completion of the induction RCT. The muscle had to be seen on specimens. Histologically complete response was defined as the absence of residual tumor cells in the tumor bed or surroundings biopsies.

Patients with persistent tumors underwent radical cystectomy with pelvic node dissection. The first pts were all operated 5 weeks after the induction RCT regardless of the response to treatment. After removing 23 bladders without any residual tumor in the specimen, we revised the initial protocol and suggest the conservative strategy in case of a histologically complete response with additional chemoradiotherapy.

When bladder-preserving chemoradiotherapy was decided, a 20-Gy boost was delivered to the bladder according to the planned dosimetry, using a three-field technique (two lateral and one anterior field). All portals were treated twice on days 64, 66, 78, and 80. Each fraction delivered 2.5 Gy, with a 6-h interval between both daily fractions. The same 5-FU/cisplatin-combination schedule used for induction therapy was administered for additional therapy.

Follow-up

Clinical examination, urine cytology, cystoscopy (with biopsy if necessary), thoracoabdominopelvic CT scan were performed routinely every 6 months or at the recurrence of symptoms.

Statistical analysis

Survival data were calculated from the beginning of radiochemotherapy to the date of the first event. In absence of an event, pts still alive at the latest follow-up were censured. Disease-free survival with functional bladder was defined as survival without any invasive relapse (locoregional relapse or distant metastasis) and any toxicity of grade more than two. Late toxicity was reported and scored according to the RTOG/European organization for the research and treatment of cancer (EORTC) late radiation morbidity scoring schema. Acute toxicity was scored according to the common terminology criteria for adverse events (version 4) scale (CTCAE v4.0).

Data were evaluated in a univariate study using contingency-table analysis and the Chi^2 test (with Yates adjustment or with Fisher's exact test when the number the pts was too small) for qualitative data, and Student test (or Mann–Whitney–Wilcoxon when the number of pts was too small) for quantitative data. Survival curves were calculated by the Kaplan–Meier method and compared by log-rank testing. Univariate analysis used the log-rank test for qualitative covariates and the univariate Cox model for quantitative covariates. Covariates with p-value <0.2 in univariate analysis were tested in a multivariate analysis using multivariate Cox

proportional hazard regression. The following covariates were included in the multiple regression model: age, sex, T stage, presence of hydronephrosis, presence of Cis, or lymphovascular space involvement (LVSI), whether the initial TUR was complete or not, histologic response to initial radiochemotherapy, type of chemotherapy, 2D vs. 3D radiotherapy. All statistical comparisons were two-sided, and p-value <0.05 was considered statistically significant.

Results

Patients

From January 1988 to December 2013, 313 pts with non-metastatic MIBC considered eligible for surgery were treated according to a conservative strategy with TMT and were included in the study. Patient and tumor characteristics are listed in Table 1. The median follow-up was 59 months (interquartile range (IQR): 26–103).

All pts were treated by induction radiochemotherapy, with 230 (73%) receiving the planned Cisplatin – five-FU chemotherapy. Other protocols used are summarized in Table 1. No patient received induction chemotherapy before concomitant radiochemotherapy.

Response to induction radiochemotherapy

All pts underwent control TURBT with systematic deep biopsies 6 weeks after the end of initial RCT. A complete histologic response was achieved for 259 pts (83%), 54 pts (17%) had a persistent tumor and were considered as non-responders (Figure 1). Fifty-four pts (17%) had a persistent tumor and were considered as non-responders. Among them, TURB showed 19 non-invasive tumors (pT1 or Cis) and 21 invasive residual tumors. The invasive character of the residue had no impact on survival. The invasion could not be defined for 14 patients because the bladder muscle was not present in the specimens.

In multivariate analysis, the absence of previous superficial bladder cancer history ($p = 0.009$) and complete initial TURBT ($p = 0.0001$) were significantly related to histologic response after induction therapy. Details are listed in Table 2.

Patients' distribution according to the additional treatment is summarized in Figure 1.

Among the 54 pts with persistent tumors, 42 underwent radical surgery with pelvic lymph node dissection and 12 refused the planned surgery. The latter was treated with additional radiochemotherapy with the same regimen as the responder pts. Among the 42 surgical pts, 22 (52%) had radical prostatocystectomy, four (10%) had anterior pelvectomy, and 16 (38%) had radical cystectomy. Histologic examination of the bladder showed invasive tumors in 29 (69%) pts (8ypT2, 19ypT3, and 2ypT4) with nodal involvement in eight (24%) cases, non-invasive tumors (ypT1*N*0) in four pts, and no residual tumor (ypT0*N*0) in one patient. Definitive histology was missing for eight pts.

Table 1. Patients' characteristics.

Characteristics	Number of pts $N = 313$(%)
Sex	
Female	59 (18.9)
Male	254 (81.1)
Age at diagnosis (years)	
Range	67.3 ± 9.3
Median [1er Q; 3e Q]	68.3 [62.1; 73.8]
≤65	124 (39.6)
>65 and <75	130 (41.5)
≥75	59 (18.9)
Extremes	36–87
Clinical T stage	
T2	261 (83.4)
T3	52 (16.6)
Lymphovascular space involvement (LVSI)	
Yes	46 (14.7)
No	258 (82.4)
Unknown	9 (2.9)
Tumor associated Cis	
Yes	24 (7.7)
No	280 (89.4)
Unknown	9 (2.9)
Hydronephrosis	
Yes	61 (19.5)
No	252 (80.5)
Number of initial TURBT	
1	266 (85.0)
2	45 (14.4)
Unknown	2 (0.6)
Residual tumor before radiochemotherapy	
Yes	71 (22.8)
No	226 (72.4)
Unknown	15 (4.8)
History of noninvasive BC	
Yes	59 (18.9)
No	186 (59.4)
Unknown	68 (21.7)
WHO performance status at diagnosis	
0	173 (55.3)
1	83 (26.5)
Unknown	57 (18.2)
Creatinine at diagnosis (micromol/L)	
Range	86 ± 20
Median	82 (73–96)
Extremes	51–172
Chemotherapy	No. of pts (%)
5-FU-CDDP	230 (73.7)
Carboplatin 5-FU	46 (14.7)
CDDP	16 (5.1)
Carboplatin	4 (1.3)
5-FU	2 (0.6)
modified CDDP-5-FU	14 (4.5)

Cis: carcinoma *in situ*; BC: bladder cancer; TURB: transurethral resection of bladder; 5FU: 5-fluorouracil; CDDP: cisplatin isaccuratea.

Among the 259 patients with complete tumor regression, 236 (91%) were treated by additional chemoradiotherapy and 23 (9%) underwent total cystectomy.

Long-term outcomes

One hundred twenty-eight pts (41%) died during follow-up. The actuarial five-year and 7-year overall survival (OS) rates were 69% (63–74) and 62% (56–68) respectively.

Factors associated with OS are summarized in Table 3. In multivariate analysis, age at diagnosis >75 years ($p = 0.024$) and response to induction RCT ($p = 0.001$) remained significant predictors for OS (Figure 2). After an adjustment on confounding factors, there was no significant difference in 5-year survival between responders treated by

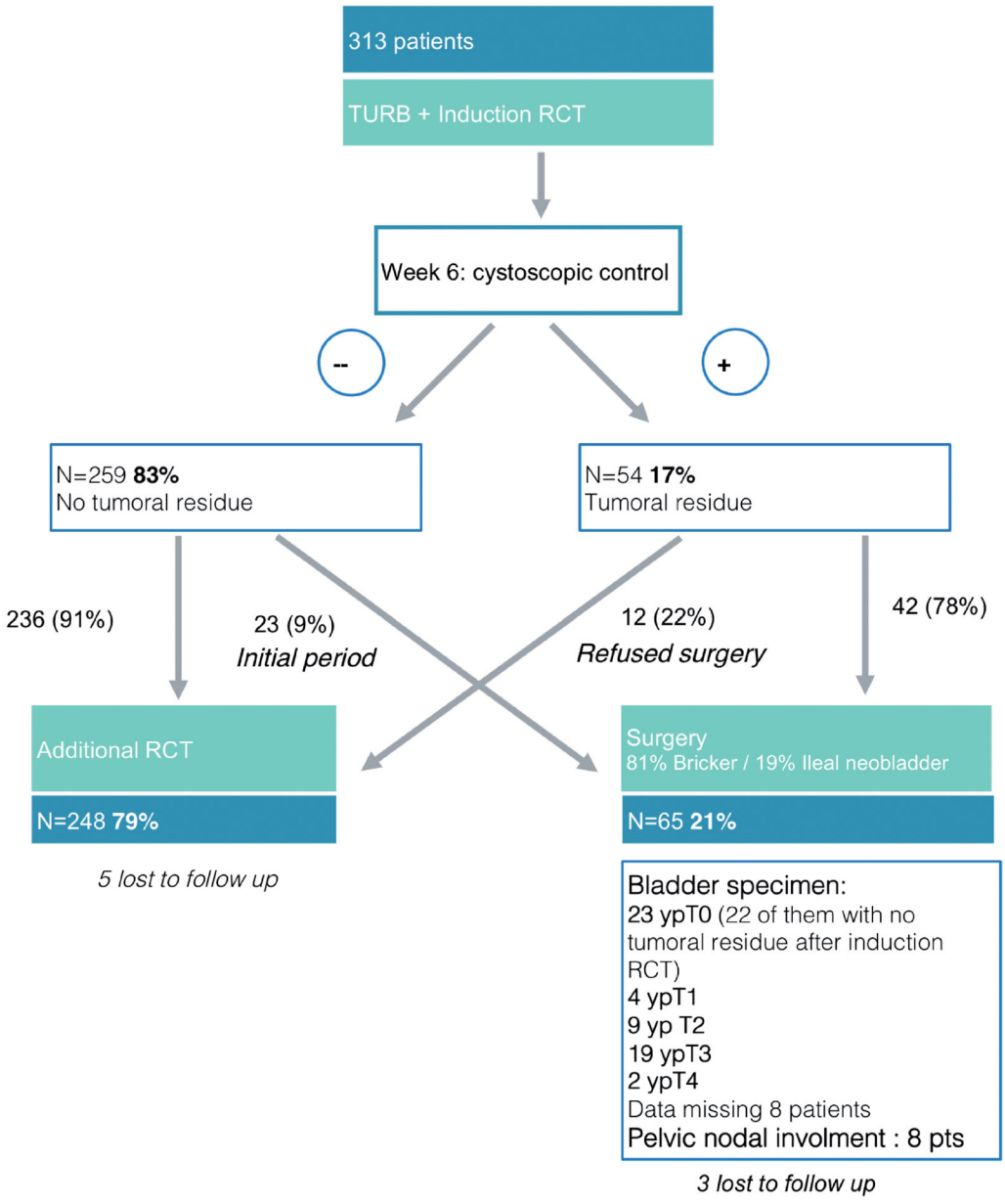


Figure 1. Consort diagram. RCT: radiochemotherapy.

radiochemotherapy (77% (71–83)) and responders treated by surgery (72% (53–91), $p = 0.233$).

Overall, 103 pts (33%) had a local and/or distant invasive recurrence with an 18-month median occurrence. Local, pelvic, and distant recurrences were seen in 47 pts (15%), 25 pts (8%), and 47 pts (15%) respectively. The actuarial five-year invasive disease-free survival rate (iDFS) was 61% (55–68). Factors associated with iDFS are summarized in Table 3. In multivariate analysis, the 5-year iDFS was significantly lower in non-responders than in responders (73% vs. 46%, HR 3.6 (2.3; 5.6), $p < 0.0001$)).

Sixty-eight pts (22%) presented distant metastasis with an 18-month median occurrence. The 5-year metastatic disease-free survival (mDFS) rate was 78%. Factors associated with mDFS are summarized in Table 3.

Among the 248 pts treated by radiochemotherapy, the actuarial 5 and 7-year intact-bladder OS was 69% (63–76) and 65% (58–72). In univariate and multivariate analysis, hydronephrosis was significantly correlated with a lower intact-bladder OS (at 5 years: 50% vs. 64%, HR 1.9 (1.1; 3.2), $p = 0.027$).

First loco-regional recurrences and their treatment

In the RCT group, ninety-four pts (30%) developed loco-regional recurrences: 35 (conservative strategy, 14%) cases of non-invasive bladder tumor with a 24-month median occurrence, 38 (conservative strategy, 15%) cases of invasive bladder cancer with a 22-month median occurrence and 21 pelvic nodal recurrences associated with distant metastasis in 10 cases.

Non-invasive bladder recurrences were treated by TURBT followed by intravesical Bacillus Calmette–Guerin (BCG) in 31

Table 2. Regression model of variables associated with response to induction radiochemotherapy (RCT).

	Univariate analysis			Multivariate analysis	
Residual tumor after induction RCT	No $N = 259$ (83%)	Yes $N = 54$ (17%)	*p*-value	OR (IC 95%)	*p*-value
Clinical T stage					
T2	222 (86)	39 (72)	0.015		
T3	37 (14)	15 (28)			
Tumor associated LVSI					
Yes	34 (74)	12 (26)	0.093		
No	217 (84)	41 (16)			
Tumor associated Cis					
Yes	18 (7)	6 (11)	0.397		
No	233 (93)	47 (89)			
History of noninvasive BC					
Yes	43 (21)	16 (40)	0.01	2.58 (1.08; 6.14)	0.032
No	162 (79)	24 (60)		1	
Sex					
Female	51 (20)	8 (15)	0.405		
Male	208 (80)	46 (85)			
Hydronephrosis					
Yes	45 (17)	16 (30)	0.039		
No	214 (83)	38 (70)			
Residual tumor before induction RCT					
Yes	46 (19)	25 (47)	<0.0001	4.33(1.68; 11)	0.002
No	199 (81)	28 (53)		1	
Chemotherapy					
5-FU-CDDP	190 (74)	40 (74)	0.589		
5-FU-carboplatin	37 (14)	9 (17)			
CDDP	14 (5)	2 (4)			
Carboplatin	3 (1)	1 (2)			
5FU	1 (0.4)	1 (2)			
Modified 5-FU CDDP	13 (5)	1 (2)			
Age (years)	67.3 ± 9.3	66.9 ± 9.6	0.731		

5FU: 5-fluorouracil; CDDP: cisplatin; LVSI: lymphovascular space involvement; BC: bladder cancer; Cis: carcinoma *in situ*; RCT: radiochemotherapy.

cases without additional toxicity, total cystectomy in four cases. MIBC recurrences were treated by total cystectomy with an external diversion in 34 cases, exclusive TURBT in two cases, partial cystectomy in one case or with chemotherapy because synchronous metastasis in one case. No correlation between non-invasive bladder recurrence and others covariables, especially presence of CIS, hydronephrosis or completeness of initial TURBT, has been found.

Acute toxicity

There was no death related to chemoradiotherapy. Treatment was well tolerated even in older pts. Grade 3 or greater acute toxicities were exclusively hematologic. One patient had a severe life-threatening grade 4 hematologic toxicity, probably related to a dihydropyrimidine dehydrogenase deficiency.

Late toxicity

There was no grade 4 or 5 toxicity during follow-up.

Among pts treated with exclusive radiochemotherapy, 10 (4%) had grade three urinary toxicity, mostly dysuria and pollakiuria and two cases of hematuria. Total cystectomy had to be performed in six pts because of nonfunctional bladder.

For the entire cohort, grade 3 intestinal toxicity was reported in four cases (rectal bleeding, colovesical fistula, or severe proctitis with small bowel obstruction requiring surgery). Two pts developed bone fatigue fractures after radiotherapy.

Discussion

To our knowledge, this study reported one of the largest series of pts treated with TMT. This large homogenous cohort, with stage cT2-T3N0M0 treated with a conservative strategy, showed encouraging long-term outcomes with 5-year OS and iDFS rates of respectively 69% and 61%. More than two-thirds of responders treated RCT alone had a functional and intact bladder after five years. These results are consistent with other large studies including the RTOG pooled analysis and experiments from Erlangen and Boston [8–10]. In the updated MGH series, the 5-year bladder-intact disease-specific survival rate was 52%; in the RTOG pooled analysis, 80% of pts alive after 5 years had an intact bladder [8,10].

In our series, 83% of pts had a complete pathologic response after TURB and induction RCT. This result compared favorably with other cohorts with rates between 55% and 93% [12,13]. Assessments of the response can be performed immediately after induction radiochemotherapy (40–45Gy) or a few weeks after the end of treatment (60–65Gy). The early assessment strategy detects non-responders more rapidly for salvage surgery but "slow responders" will be wrongly operated. Conversely, the late assessment strategy can delay salvage surgery, causing it to become more difficult after a higher radiation therapy dose.

Table 3. Regression model of variables associated with invasive disease-free survival and metastatic disease-free survival.

	Disease-free survival			Metastatic disease-free survival			Overall survival		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
Variable	*p*-value	Risk ratio	Adj. *p*-value	*p*-value	Risk ratio	Adj. *p*-value	*p*-value	Risk ratio	Adj. *p*-value
Sex	0.73			0.89			0.82		
Age									
≤65 years								1	
>65 years and <75 years	0.88			0.98			0.025	1	
≥75 years								1.6 (1.1; 2.5)	0.024
T stage (2009 classification)									
T2	0.02		0.055	0.011		0.051	0.302		
T3									
LVSI present									
Yes	0.46			0.085		0.25	0.513		
No									
Cis present	0.48			0.87			0.549		
Yes									
No									
Hydronephrosis									
Yes	0.07		0.34	0.016		0.16	0.047		0.07
No									
Residual tumor before RCT	0.59			0.26			0.158		0.51
Yes									
No									
History of NIBMT									
Yes	0.45		0.061	0.38		0.136	0.88		
No									
Residual tumor (half-treatment)									
Yes	<0.0001	3.61 (2.33; 5.60)	<0.0001	<0.0001	3.43 (1.78; 6.6)	0.0002	<0.0001	2.6 (1.5; 4.4)	0.001
No		1			1			1	
Chemotherapy type									
Standard									
Carboplatin 5FU									
CDDP only									
Carboplatin only	0.32			0.698			0.7		
5FU only									
"Modified" standard									

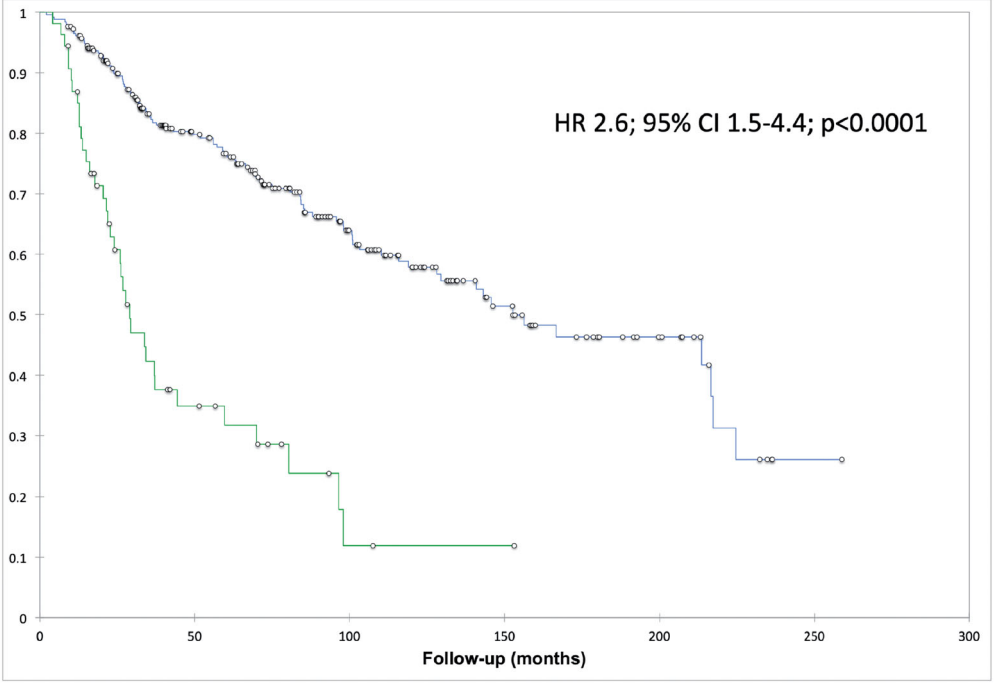
5FU: 5-fluorouracil; CDDP: cisplatin; LVSI: lymphovascular space involvement; BC: bladder cancer; Cis: carcinoma *in situ*; RCT: radiochemotherapy; NIMBT: non-invasive muscle bladder tumor

In our experiment, a macroscopically complete TURBT before the beginning of RCT appears to be a major prognostic factor for response to RCT. This feature was found by others [8,10,14]. Clinical T stage and hydronephrosis were also associated with response in our series as well as other cohorts [10,15,16]. Surprisingly, we reported a correlation between a persistent tumor after induction radiochemotherapy and a previous history of non-invasive MIBC, which could be explained by a more resistant tumor profile and be used to select candidates for conservative treatment. The size of tumors was not known in our study but could be a prognostic factor to consider [17].

Response to induction RCT is the major prognostic factor in all conservative treatment studies. In our series, 5-year OS was respectively 77% in responders vs. 32% in non-responders. The prognosis was very poor in non-responders despite salvage surgery. Several hypotheses can be discussed: first, the elapsed time between the beginning of treatment and surgery could contribute to tumor progression and increase the risk of metastasis. Secondly, RCT could select aggressive tumors with pejorative molecular and genomics features. This hypothesis seems to be the most relevant, considering the considerable advances in defining different molecular subtypes of bladder cancer in the past ten years and their importance in outcome prediction [18].

Despite encouraging long-term results, conservative RCT is not an international standard treatment in routine practice, particularly for the youngest pts. Indirect historic comparison between surgical and radiochemotherapy series implies many biases in patient selection and tumor staging [19,20]. In a monocentric retrospective trial, Kulkarni et al. used a propensity scored matched-cohort and found similar 5-year OS in the surgery and TMT groups [21]. In any case, the point is not to compare surgery to conservative TMT but to select a subset of pts who are good candidates for conservative strategy.

After RCT, the risk of local recurrence ranges from 10 to 40% [6,22,23] . These rates highlight the need for scheduled cystoscopies to rapidly detect local recurrences. Non-invasive bladder recurrences can be treated with TURBT and intravesical BCG. In our experience, there was no increased toxicity of BCG performed after bladder irradiation. In the MGH cohort, 5-year OS was similar between invasive and non-invasive recurrence groups but 5-year bladder intact OS was lower [23]. Invasive recurrences must be treated by salvage cystectomy in medically operable pts. Several series found similar mortality rates and complications after salvage surgery as compared to immediate cystectomy [22,24]. In our experience, among the 41 operated pts because of isolated local recurrence (first event in 34 pts and invasive recurrence after



	Follow-up (months)	50	100	150	200	250
At risk	Complete response	154	80	35	15	1
	Persistent tumor	13	2	1	0	0

Figure 2. OS according to initial RCT response (blue curve: complete histologic response, green curve: persistent tumor).

NIMIBC recurrence in seven pts) we reported one death related to infectious complications. Published data showed a salvage cystectomy rate of 20 to 30% combining immediate surgery for no response post-chemoradiation or delayed surgery for local recurrence [6]. In Erlangen's cohort, a 10-year specific survival rate was 45% for pts operated for a local recurrence [9]. In our series, this rate was 60% at 5 years (data not shown).

Quality of life (Qol) with a functional intact bladder is one the most important aim of TMT. In the pooled analysis of RTOG trials, authors noted 7.6% late grade 3 toxicity, consistent with toxicities reported in our series [25]. Six pts underwent salvage cystectomy due to nonfunctional bladder, which is concordant with other trials [9,10]. Unfortunately, QoL assessment was not performed in our study with validated tools. Only 34 pts filled in an institutional questionnaire with a 30 month-average time after TMT: for 92% of interviewed pts, QoL was considered as satisfying or very satisfying (data are not shown). In the French multicentric trial Getug 97-015, 70% of pts had a satisfying QoL [26]. Mak et al., in a cross-sectional study, evaluated long-term QoL comparing cystectomy and TMT: TMT was associated with the better patient-reported general QoL, sexual function, and body image [27].

The optimal TMT modalities are not clearly defined. The English BC2001 trial concluded that radiochemotherapy is superior to radiation alone but the best concomitant chemotherapy remains to be defined [28]. Although benefits of neoadjuvant chemotherapy were pointed out before cystectomy, its role before RCT is uncertain [29]. In the same way, several phases I–II adjuvant chemotherapy trials failed to demonstrate impact on survival in comparison to radiochemotherapy alone [28,30]. Regarding the radiotherapy regimen, we used a special bi-fractionated split-course schedule, delivering 24 Gy in the induction RCT (i.e., equivalent to 40–45Gy in standard fractionation according to the linear-quadratic model with an alpha/beta ratio of 10 Gy) and up to 44 Gy (i.e., equivalent to 60–66Gy in standard fractionation. This has the theoretical advantage of decreasing harm to normal tissue. This choice was also supported by some studies in rodent tumors which had demonstrated an increase in tumor cell growth 10 to 15 d after exposure to a cytotoxic treatment and suggested enhanced tumor cell killing when the cytotoxic event was repeated every 2 weeks [31]. Moreover, an optimal effect of the cisplatin/x-ray synergy had been observed when a radiation split dose was used concurrently with cisplatin exposure [32]. Very recently, a meta-analysis of individual patient data from pts with locally advanced bladder cancer enrolled in two multicenter, randomized, controlled, phase III trials done in the UK: BC2001 and BCON showed that the hypo-fractionated schedule of 55 Gy in 20 fractions is non-inferior to the standard of 64 Gy in 32 fractions with regard to both invasive locoregional control and toxicity and is superior with regard to

invasive locoregional control [33]. Accelerated hyperfractionated radiotherapy has also been evaluated in some trials with a possible benefice and is compared to standard fractionation in ongoing phase II RTOG 0712 [14,34].

In conclusion, this radiochemotherapy combination with concomitant bifractionated split-course radiotherapy is easy to implement and well-tolerated. Over the years, our experience in the TMT enabled us to improve the selection of the good candidates for conservative treatment: pts with unifocal cT2N0 tumor, without Cis or hydronephrosis or NMIBC history, and who achieve macroscopic complete TURB before beginning RCT. In this selected population, regardless of age, in which the complete response rate is high and the 5-year intact-bladder survival very similar to surgical series, cystectomy might be omitted with the TMT approach. Research is ongoing to improve this conservative strategy by adding targeted therapies or immune modulators and by identifying biomarkers for further refining patient selection [35,36].

Disclosure statement

No potential conflict of interest was reported by the author(s).

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