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Original Article

Recommendations for planning and delivery of radical radiotherapy for localized urothelial carcinoma of the bladder

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ABSTRACT

Purpose: Curative radio-chemotherapy is recognized as a standard treatment option for muscle-invasive bladder cancer (MIBC). Nevertheless, the technical aspects for MIBC radiotherapy are heterogeneous with a lack of practical recommendations.

Methods and materials: In 2018, a workshop identified the need for two cooperative groups to develop consistent, evidence-based guidelines for irradiation technique in the delivery of curative radiotherapy. Two radiation oncologists performed a review of the literature addressing several topics relative to radical bladder radiotherapy: planning computed tomography acquisition, target volume delineation, radiation schedules (total dose and fractionation) and dose delivery (including radiotherapy techniques, image-guided radiotherapy (IGRT) and adaptive treatment modalities). Searches for original and review articles in the PubMed and Google Scholar databases were conducted from January 1990 until March 2020. During a meeting conducted in October 2020, results on 32 topics were presented and discussed with a working group involving 15 radiation oncologists, 3 urologists and one medical oncologist. We applied the American Urological Association guideline development's method to define a consensus strategy.

Results: A consensus was obtained for all 34 except 4 items. The group did not obtain an agreement on CT enhancement added value for planning, PTV margins definition for empty bladder and full bladder protocols, and for pelvic lymph-nodes irradiation. High quality evidence was shown in 6 items; 8 items were considered as low quality of evidence.

Conclusion: The current recommendations propose a homogenized modality of treatment both for routine clinical practice and for future clinical trials, following the best evidence to date, analyzed with a robust methodology. The XXX group formulates practical guidelines for the implementation of innovative techniques such as adaptive radiotherapy.

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Radical cystectomy with cisplatin-based neoadjuvant chemotherapy is considered the standard of care to treat localized urothelial muscle-invasive bladder carcinoma (MIBC), providing 5-year overall survival (OS) rates of more than 50% among fit patients [1,2].

Historically, "curative" radiotherapy was proposed as an alternative to radical cystectomy for patients deemed unfit for surgery and/or with inoperable MIBC [3,4].

Concerns about morbi-mortality as well as impact on quality of life following radical cystectomy have led to the development of organ-preserving approaches even in patients fit for surgery. In this context, transurethral resection of bladder tumors (TURBT) followed by curative radiotherapy with concomitant chemotherapy (with or without neoadjuvant/adjuvant chemotherapy), known as

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the trimodal therapy strategy, has emerged as a relevant bladder-preserving approach. Although the only phase III randomized trial comparing radical cystectomy to trimodal therapy has failed to accrue [5], trimodal therapy has long been proposed by several teams and recommended as an alternative for fit patients, with similar oncological results [2,6,7], acceptable toxicity [8] and an overall preserved quality of life and quality of conserved bladder function [9–11].

Trimodal therapy can be proposed as an alternative to radical cystectomy in a well selected population of patients with tumor stage T2–T3 (+/−T4a) N0M0, no multifocal lesions, no hydronephrosis and no extensive in-situ carcinoma (CIS) outside the area of involvement[12]. However, we note that these prognostic and predictive factors come from phase II prospective trials as well as retrospective studies with radiotherapy-only strategies in many cases [6,13–16], so they must be regarded with caution when it comes to proposing or declining an organ-preservation strategy. Besides, patients eligible for trimodal therapy must have an adequate bladder function; no consensus exists on this criteria, but this may include: bladder capacity >200 ml, no significant incontinence ($\leq$1 pad/day), no significant irritative symptoms (no urgency, no daily pollakiuria, nocturnal pollakiuria $\leq$2/night) and no significant dysuria (IPSS score <8). Notably, the role of trimodal therapy for patients with high-risk non-muscle-invasive bladder cancer or with history of BCG failure remains controversial, and this strategy cannot be recommended in routine for these patients for now [17]. In any case, the feasibility of trimodal therapy should be validated during a multidisciplinary tumor board, involving urologists, medical oncologists, pathologists, radiologists and radiation oncologists.

The aims of the current work were to review the modalities of curative radiotherapy within trimodal therapy for localized MIBC, to homogenize this treatment delivery across the group of institutions that are or will start performing this technique and subsequently to propose an optimal radiotherapy technical consensus.

Methods

In 2018, a workshop identified the need for two cooperative groups to develop evidence-based guidelines for the delivery of curative radiotherapy for localized MIBC, both for routine clinical practice and for the implementation of future clinical trials. In this perspective, the approach used to conduct the consensus methodology research was a consensus development panel [18].

To do so, two radiation oncologists (JK and PS) first performed a review of the literature addressing several topics relative to radical bladder radiotherapy: planning Computed Tomography (CT) acquisition, target volume delineation, radiation schedules (total dose and fractionation), dose delivery (including radiotherapy techniques, image-guided radiotherapy (IGRT) and adaptive treatment modalities) and concurrent systemic treatment. Patient selection criteria for the indication of trimodal therapy was not in the scope of this review.

Searches for original and review articles in the PubMed and Google Scholar databases were conducted from January 1990 until March 2020. General search terms (including both Medical Subject Headings (MeSH) and free text words) included the following: "bladder cancer", "radiotherapy", "trimodal therapy", "chemoradiotherapy", "bladder-sparing", "dose constraints", "image-guided radiotherapy", and "adaptive radiotherapy". Individual reference lists were reviewed for additional relevant references.

Due to the heterogeneity of populations (e.g. patients with either resectable or unresectable tumors) and of regimens for bladder radical radiotherapy, the employed methodology was:

- to focus uniquely on bladder-sparing trimodal therapy (not palliative) prospective trials of $\geq$20 patients to address the question of (chemo)radiotherapy regimens and correlated clinical outcomes;
- to extend the review to relevant retrospective series of radical bladder radiotherapy (with or without chemotherapy) to address more technical aspects of the treatment (CT acquisition, target volumes delineation, and radiotherapy dose delivery).

Once this review was performed, results on each topic were presented by JK and PS (Tables 1–3) and discussed during a meeting conducted in October 2020 with a working group involving 15 radiation oncologists. Additionally, three urologists and one medical oncologist were solicited for their expertise in two topics regarding TURBT and concurrent systemic treatment, respectively. We applied the American Urological Association guideline development's method to categorize the statements [19].

For each topic, a blinded vote was performed among the experts to determine:

- the evidence strength: A – high quality evidence (well-conducted randomized clinical trials (RCTs), exceptionally strong observational studies); B – moderate quality evidence (RCTs with some weaknesses, generally strong observational studies); and C – low quality evidence (observational studies that provide conflicting information or design problems (such as very small sample size).
- the recommendation grade: strong (1), moderate (2) or weak (3).

The final evidence strengths and recommendation grades corresponded to those proposed by the majority of the panelists. In the absence of majority reached following the first vote, a second blinded vote was proposed after a brief summary of the available data on the field by JK and PS.

A summary of the guidelines from the working group is presented after the review (Table 4).

Results

Transurethral resection of bladder tumors (TURBT) preceding radiotherapy

TURBT is the first step of a trimodal therapy. TURBT can be performed either by monopolar or bipolar, en bloc or standard resection [20]. A wider margin of tumor-free urothelium around the lesion is required. The depth of the resection is crucial, often down to the peri-vesical fat, despite the risk of bladder perforation. As such, the bladder catheter is removed between Day 2 and Day 8 after the procedure. In the case of large tumors in patients not eligible for radical surgery, resection must be maximal if it cannot be complete.

During the TURBT procedure, a special attention should be paid to bi-manual pelvic exam under anesthesia (EUA), as pre- and post-resection EUA constitute a component of the clinical staging of the lesion [21]; palpable tumor on the outer surface of the bladder following TURBT is in favor of T3 or T4 disease, depending on it is mobile or fixed, respectively.

The quality of TURBT in a trimodal therapy setting has been assessed in several prospective studies, and achieving complete TURBT is crucial for oncological outcomes. Giacalone et al. [6] compiled the pooled results from prospective trials led by the Massachussets General Hospital [22–29]; complete TURBT was associated with increased bladder-intact disease-specific survival compared to incomplete resection (HR = 0.72, P = 0.02). The time interval between TURBT and radiotherapy has not been addressed

Table 1
Phase II and phase III trials (≥20 patients) of bladder-sparing trimodal therapy for muscle-invasive bladder cancer: patients and treatment.

Reference	Name of study/ arm	Design/follow-up	N	Stage	WBRT: total dose	WBRT: dose per fraction	Index tumor RT: total dose (if different)	Index tumor RT: dose per fraction for the complement (if different)	PLNRT: total dose (upper limit)	PLNRT: dose per fraction	Split vs Cont.	OTT weeks	Modality of RT	ART	Concurrent systemic treatment	NAD/AD chemotherapy
Lagrange (2011)	GETUG 97015	Phase II 8 years	53	T2-T4a N0/Nx	63 Gy	1.8–2 Gy qd	–	–	45 Gy (L5-S1)	1.8 Gy qd	Split	6.5	2D/3D	No	CDDP-5FU × 3C	No
Tester (1993)	RTOG 8512	Phase II 36 months	48	T2-T4 N0/ N1N2 (8%)	60GyGy	2 Gy qd	–	–	40 Gy (L5-S1)	2 Gy qd	Split	9	2D/3D	No	CDDP × 3C	No
Shipley (1998)	RTOG 8903	Phase III 5 years	74	T2-T4a N0/Nx	39.6 Gy	1.8 Gy qd	64.8 Gy	1.8 Gy qd	39.6 Gy (S2-S3)	1.8 Gy qd	Split	9	2D/3D	No	CDDP × 3C	NAD: 50% MCV × 3C
Gogna (2006)	TROG 9701 & TROG 9906	Phase II × 2 23 months	113	T1-T4 N0	63–64 Gy (65%) 50–50.4 Gy (25%)	1.8 Gy-2 Gy qd	– 63–64 Gy	– 1.8 Gy qd	–	–	Cont.	6.5–7	2D/3D	No	CDDP weekly	No
Hoskin (2010)	RT vs RT + CON Arm B (exp)	Phase III 5 years	164/ 327	T1-T4b N0	64 Gy (30%) (or 55 Gy (70%))	2 Gy qd (or 2.75 Gy qd)	–	–	–	–	Cont.	6.5 (or 4)	2D/3D	No	CON (arm B)	No
James (2012)	BC 2001 Arm B (exp)	Phase III 70 months	182/ 320	T2-T4a N0	64 Gy (61%) (or 55 Gy (39%))	2 Gy qd (or 2.75 Gy qd)	–	–	–	–	Cont.	6.5 (or 4)	2D/3D	No	5FU - MMC × 2C (arm B)	NAD: 31%
Kragelj (2005)		phase II 10.3 years	84	T1-T4 N0	63.8–64 Gy	1.8–2.2 Gy qd	–	–	46–46.2 Gy (NR)	1.8–2.2 Gy qd	Cont.	6–6.5	2D/3D	No	Vinblastine weekly	No
Eapen (2004)		phase II 34 months	200	T1-T4b N0/N+ (7%)	60 Gy	2 Gy qd	–	–	40 Gy (NR)	2 Gy qd	Cont.	6	2D/3D	No	Intra-arterial CDDP × 2c	NAD: intra-art. CDDP × 1C
Tester (1996)	RTOG 8802	phase II 3 years	93	T2-T4a N0/N+ (6%)	39.6 Gy	1.8 Gy qd	64.8 Gy	1.8 Gy qd	39.6 Gy (L5-S1)	1.8 Gy qd	Split	9	2D/3D	No	CDDP × 3C	NAD: MCV × 3C
Fellin (1997)		phase II 46 months	56	T2-T4 N0	41.4 Gy	1.8 Gy qd	64.8 Gy	1.8 Gy qd	41.4 Gy (S1-S2)	1.8 Gy qd	Split	9	2D/3D	No	CDDP × 3C	NAD: MCV × 2C
Caffo (2011)		phase II 74 months	26	T2-T4 N0	36 Gy	1.8 Gy qd	54 Gy	1.8 Gy qd	36 Gy (S1-S2)	1.8 Gy qd	Cont.	6	2D/3D	No	Gem CDDP weekly	No
Arias (2000)		phase II	50	T2-T4 N0	45 Gy	1.8 Gy qd	65 Gy	2 Gy qd	45 Gy (L5-S1)	1.8 Gy qd	Split	8	2D/3D	No	CDDP d1-d5	NAD: MVAC × 2C
Coen (2019)	RTOG 0712 Arm Gem	Phase II 4.3 years	35/ 70	T2-T4a N0	52 Gy	2 Gy qd	64 Gy	2 Gy qd	44 Gy (NR)	2 Gy qd	Split	9	2D/3D	No	Gem twice weekly	AD: Gem CDDP × 4C
Lin (2009)		Phase II 47 months	30	T2-T4a N0	50.4 Gy	1.8 Gy qd	64.8 Gy	1.8 Gy qd	45 Gy (S2-S3)	1.8 Gy qd	Split	7	2D/3D	No	CDDP weekly (52%) CDDP-paclitaxel weekly (48%)	NAD: CDDP-5FU × 3C (52%) CDDP-5FU-Paclitaxel × 3C

(*continued on next page*)

Table 1 (*continued*)

Reference	Name of study/ arm	Design/follow-up	N	Stage	WBRT: total dose	WBRT: dose per fraction	Index tumor RT: total dose (if different)	Index tumor RT: dose per fraction for the complement (if different)	PLNRT: total dose (upper limit)	PLNRT: dose per fraction	Split vs Cont.	OTT weeks	Modality of RT	ART	Concurrent systemic treatment	NAD/AD chemotherapy
																(48%)
Mokarim (1997)		Phase II 45 months	35	T2-T4 N0	40 Gy	2 Gy qd	60 Gy	2 Gy qd	40 Gy (L5-S1)	2 Gy qd	Split	8	2D/3D	No	Intra-arterial CDDP - doxorubicin × 3C	No
Tunio (2012)		Phase III 5 years	230	T2-T4 N0	45 Gy	1.8 Gy qd	65 Gy	2 Gy qd	Arm A: 45 Gy (L5-S1) Arm B: No	Arm A: 1.8 Gy qd Arm B: No	Cont.	7	2D/3D	No	CDDP weekly	No
Murthy (2016)		Phase II 30 months	44	T1-T4 N0	64 Gy	2 Gy qd	68 Gy (55%)	2.12 Gy qd (SIB)	55 Gy (73%) (L5-S1)	1.72 Gy qd	Cont.	6.5	IMRT	Yes	CDDP weekly	NAD: 36% Gem Carboplatin
Hagan (2003)	RTOG 9706	Phase I-II 26 months	47	T2-T4a N0	45.6 Gy I = 21.6gy C = 24 Gy	I = 1.8 Gy qd C = 1.5 Gy bid	64.8 Gy I = 40.8gy C = 24 Gy	I = 1.8 Gy-1.6 Gy bid C = 1.5 Gy bid	45.6 Gy I = 21.6gy C = 24 Gy (NR)	I = 1.8 Gy qd C = 1.5 Gy bid	Split	8	2D/3D	No	CDDP 2d/week	AD: MCV × 3C
Kaufman (2009)	RTOG 9906	Phase I-II 50 months	80	T2-T4a N0	52.3 Gy I = 28.3 Gy C = 24 Gy	I = d1-d5: 1.6 Gy-1.5 Gy bid d8-d17: 1.6 Gy qd C = 1.5 Gy bid	64.3 Gy I = 40.3 Gy C = 24 Gy	I = 1.6 Gy-1.5Gybid C = 1.5 Gy bid	44.8 Gy I = 20.8 Gy C = 24 Gy (S1-S2)	I = 1.6 Gy qd C = 1.5 Gy bid	Split	9	2D/3D	No	CDDP – placitaxel weekly	AD: Gem CDDP x4C
Mitin (2013)	RTOG 0233	Phase II 5 years	97	T2-T4a N0	52.3 Gy I = 28.3 Gy C = 24 Gy	I = d1-d5: 1.6 Gy-1.5 Gy bid d8-d17: 1.6 Gy qd C = 1.5 Gy bid	64.3 Gy I = 40.3 Gy C = 24 Gy	I = 1.6 Gy-1.5Gybid C = 1.5 Gy bid	44.8 Gy I = 20.8 Gy C = 24 Gy (NR)	I = 1.6 Gy qd C = 1.5 Gy bid	Split	9	2D/3D	No	Arm A: CDDP Paclitaxel weekly Arm B: CDDP – 5FU weekly	AD: Gem CDDP Paclitaxel × 4c
Coen (2019)	RTOG 0712 Arm CDDP 5FU	Phase II 4.3 years	35/ 70	T2-T4a N0	52.3 Gy I = 28.3 Gy C = 24 Gy	I = d1-d5: 1.6 Gy-1.5 Gy bid d8-d17: 1.6 Gy qd C = 1.5 Gy bid	64.3 Gy I = 40.3 Gy C = 24 Gy	I = 1.6 Gy-1.5Gybid C = 1.5 Gy bid	44.8 Gy I = 20.8 Gy C = 24 Gy (NR)	I = 1.6 Gy qd C = 1.5 Gy bid	Split	9	2D/3D	No	CDDP – 5FU weekly	AD: Gem CDDP × 4C
Zapatero (2012)		Phase II (protocol 2) 5 years	39	T2-T4 N0	45.6 Gy I = 21.6 Gy C = 24 Gy	I = 1.8 Gy qd C = 1.5 Gy bid	64.8 Gy I = 40.8gy C = 24 Gy	I = 1.8 Gy-1.6 Gy bid C = 1.5 Gy bid	45.6 Gy I = 21.6gy C = 24 Gy (NR)	I = 1.8 Gy qd C = 1.5 Gy bid	Split	8	2D/3D	No	CDDP weekly	No
Hafeez (2016)		Phase II 19 months	20	T2T3 N0	52 Gy	1.625 Gy qd	70 Gy	2.19 Gy qd	–	–	Cont.	6.5	IMRT	Yes	5FU – MMC Gem (15%)	NAD: 70% CDDP Gem
Housset (1993)		Phase II 27 months	54	T2-T4 N0-N1 (7%)	44 Gy I = 24 Gy C = 20 Gy	I = 3 Gy bid d1, 3, 15, 17 C = 2.5 Gy bid d64, 66, 78, 80	–	–	24 Gy (L5-S1)	3 Gy bid d1, 3, 15, 17	Split	11.5	2D/3D	No	CDDP 5FU × 4C	No

Table 1 (*continued*)

Reference	Name of study/ arm	Design/follow-up	N	Stage	WBRT: total dose	WBRT: dose per fraction	Index tumor RT: total dose (if different)	Index tumor RT: dose per fraction for the complement (if different)	PLNRT: total dose (upper limit)	PLNRT: dose per fraction	Split vs Cont.	OTT weeks	Modality of RT	ART	Concurrent systemic treatment	NAD/AD chemotherapy
Kaufman (2000)	RTOG 9506	Phase I/II 29 months	34	T2-T4 N0-Nx	44 Gy I = 24 Gy C = 20 Gy	I = 3 Gy bid d1, 3, 15, 17 C = 2.5 Gy bid d64, 66, 78, 80	–	–	24 Gy (NR)	3 Gy bid d1, 3, 15, 17	Split	11.5	2D/3D	No	CDDP 5FU × 4C	No
James (2012)	BC 2001 Arm B	Phase III 70 months	182/ 320	T2-T4a N0	55 Gy (39%) (or 64 Gy (61%))	2.75 Gy qd (or 2 Gy)	–	–	–	–	Cont.	4 (or 6.5)	2D/3D	No	5FU - MMC × 2C (arm B)	NAD: 31%
Hoskin (2010)	RT vs RT + CON Arm B	Phase III 5 years	164/ 327	T1-T4b N0	55 Gy (70%) (or 64 Gy (30%)	2.75 Gy qd (or 2 Gy qd)	–	–	–	–	Cont.	4 (or 6.5)	2D/3D	No	CON (arm B)	No
Choudhury (2011)	GemX	Phase II 36 months	50	T2-T3 N0	52.5 Gy	2.5 Gy qd	–	–	–	–	Cont.	4	2D/3D	No	Gem weekly	No
Thompson (2017)	GemX/neoGemX	Phase II 16 months	78	T2-T4 N0	52.5 Gy	2.5 Gy qd	–	–	–	–	Cont.	4	2D/3D	No	Gem weekly	NAD: 49% Gem CDDP or carboplatin
Hussain (2004)		Phase II 51 months	41	T2-T4a N0Nx	55 Gy	2.5 Gy qd	–	–	–	–	Cont.	4	2D/3D	No	5FU – MMC × 2C	No

WBRT: whole bladder RT; PLNRT: pelvic lymph nodes RT; cont.: continuous; OTT: overall treatment time; ART: adaptive RT; NAD/AD: neoadjuvant/adjuvant chemotherapy; exp: experimental arm; I: induction chemoradiotherapy; C: consolidation chemoradiotherapy; NR: non reported; CDDP: cisplatin; CON: carbogen and nicotinamide; MCV: Methotrexate, cisplatin, vinblastine; Gem: gemcitabine.

Table 2
Phase II/phase III trials (≥20 patients) of bladder-sparing trimodal therapy for muscle-invasive bladder cancer: outcomes and late toxicities.

Reference	Name of study	Complete Response rate	5-year OS	5-year CSS	Salvage cystectomy rate (immediate or delayed)	Late G3 + GU toxicity	Late G3 + GI toxicity
Lagrange (2011)	GETUG 97015	NR	43% (8-year OS 36%)	NR	33%		
Tester (1993)	RTOG 8512	66%	3-year OS 64%	NR	22%	2%	2%
Shipley (1998)	RTOG 8903	60%	49%	NR	20%	11%	8%
Gogna (2006)	TROG 9701 TROG 9906	70%	NR	50%	13%	4%	2%
Hoskin (2010)	RT vs RT + CON Arm B	81%	50%	NR	8%	*39%*	*7%*
James (2012)	BC 2001 Arm B	NR	48%	NR	11%	Overall G3 + RTOG toxicity: 8% *Overall G3 + LENT/SOMA toxicity: 54%*	
Kragelj (2005)		78%	9-year OS 25%	9-year CSS 51%	8%	*9-year prevalence 66%*	9-year prevalence 11%
Eapen (2004)		83%	50%	62%	15%	1%	0%
Tester (1996)	RTOG 8802	75%	4-year OS 62%	NR	40%	8%	7%
Fellin (1997)		50%	55%	59%	46%	2%	2%
Caffo (2011)		100%	70%	79%	15%	0%	0%
Arias (2000)		68%	48%	NR	20%	NR	NR
Coen (2019)	RTOG 0712 Arm Gem	78%	NR	NR	15%	NR	NR
Lin (2009)		77%	60%	NR	17%	3%	0%
Mokarim (1997)		74%	77%	NR	26%	9% (WHO)	0% (WHO)
Tunio (2012)		93%	52%	NR	NR	1%	0%
Murthy (2016)		100%	3-year OS 67%	3-year CSS 73%	9%	4%	0%
Hagan (2003)	RTOG 9706	74%	3-year OS 61%	NR	17%	13%	6%
Kaufman (2009)	RTOG 9906	81%	56%	71%	13%	6%	0%
Mitin (2013)	RTOG 0233	67%	73%	NR	5%	5% (CTCAE)	1% (CTCAE)
Coen (2019)	RTOG 0712 Arm CDDP 5FU	88%	NR	NR	9%	NR	NR
Zapatero (2012)		80%	60%	NR	23%	NR	NR
Hafeez (2016)		NR	NR	NR	NR	10%	0%
Housset (1993)		74%	3-year OS 59%	3-year CSS 62%	NR	NR	NR
Kaufman (2000)	RTOG 9506	67%	3-year OS 83%	NR	29%	6%	15%
James (2012)	BC 2001 Arm B	NR	48%	NR	11%	Overall G3 + RTOG toxicity: 8% *Overall G3 + LENT/SOMA toxicity: 54%*	
Hoskin (2010)	RT vs RT + CON Arm B	81%	50%	NR	8%	*39%*	*7%*
Choudhury (2011)	GemX	88%	63%	78%	8%	NR	NR
Thompson (2017)	GemX/neoGemX	92%	2-year OS 68%	NR	9%	0%	4%
Hussain (2004)		71%	36%	2-year CSS 68%	19%	NR	NR

OS: overall survival; CSS: cancer-specific survival; GU: genito-urinary; GI: gastrointestinal.

specifically; in the studies previously cited, radiotherapy started between 4 and 8 weeks following TURBT [22–29].

Planning CT-scan acquisition

Controversial data exist regarding the correlation between bladder filling and bladder motion during radiotherapy [30–32]. When considering dose to organs at risk (OARs) according to bladder filling, Majewski et al. suggested that dose distribution in the rectum and in the bowels was significantly better with a "partially empty bladder" (80 mL), as compared to a "partially full bladder" (150 mL). As expected, dose distribution in OARs was also improved when partial bladder rather than whole bladder radiotherapy is performed [32]. Overall, Dees-Ribbers et al. suggest that both empty and full bladder protocols were acceptable, and treatment choice should be based upon dose constraints to OARs. The authors recommend that [30]:

- for whole bladder single-dose level irradiation: empty bladder protocols should be used to reduce the irradiated volume;
- for index tumor irradiation (i.e. irradiation of tumor bed and/or gross residual tumor, either for partial bladder radiotherapy or when a two-dose level approach is considered sequentially or concomitantly), full bladder protocols should be used to move healthy tissues away from the irradiated volume.

Role of bladder multiparametric MRI for trimodal therapy

The use of bladder multiparametric MRI (mp-MRI) within a trimodal therapy strategy can have several objectives:

- at staging: insights in bladder mp-MRI have led to the development of VIRADS criteria, which assess the risk of extravesical extension [33], accounting for the high sensitivity and specificity to detect ≤T2 versus T3 tumor (respectively 83% (95% CI 75–88) and 87% (95% CI 78–93) [34]. This can be of interest in order: (i) to assess the ability to perform a complete TURBT and thus to confirm the indication of trimodal therapy; (ii) to help in the delineation of clinical target volume (cf. dedicated section), with decision or not to add a security margin regarding the lesion, depending on the risk of extravesical extension;
- following TURBT: in case of inability to perform complete TURBT, post-TURBT bladder MRI can help to identify residual gross disease and perivesical extension [35,36]. In this case, due to frequent post-resection scar and artifacts generally per-

Table 3
Strategies of adaptive radiotherapy for radical bladder radiotherapy.

ART strategy	Reference	Type of study	No. patients	Radiotherapy technique	Number of scanners for ART (CT/CBCT)	Bladder repletion during CT planning	Volumes and prescription doses (number of fractions)	Iso or anisotropic margins	Bladder repletion during treatment	Additional time (min)	Observed benefit
Off-Line/Composite	Pos et al. (2005)	P	21	RTC3D	CT + 5 CBCT	Full	Bladder: 60 Gy (25f) or 55 Gy (20f) PLN: 40 Gy (20f)	Iso (15 mm)	Full	N/A	– Mean irradiated volume reduced by 40% (PTVconv-PTVart)
	Foroudi et al. (2009)	P	5	RTC3D	CT + 5 CBCT	Empty	Bladder: 60 Gy (30f)	Iso (15 mm)	Empty	7	– Better coverage of CTV (V95%)
	Webster et al. (2013)	R	20	RTC3D	CT + 3 CBCT	Empty	Bladder: 52.5 Gy (20f)	Iso (Composite 1: 5 mm/Composite 2: 10 mm)	Empty	Recognized but not specified	– Better coverage of CTV (V95%) – Mean irradiated volume reduced by 14,6% to 35%
PoD non individualised	Burridge et al. (2006)	R	20	RTC3D	CT	Empty	Bladder: 52,5Gy (20f)	Aniso	Empty	Recognized but not specified	– Meanirradiated small bowel volume reduced by 31 cm3 on average
	Vestergaard et al. (2010)	R	10	RCMI	CT	Empty	Bladder: 60 Gy (30f)	Iso	Empty	N/A	– Mean volume receiving 95% of prescribed dose reduced by 30 to 40%
	Murthy et al. (2011)	R	10	Tomotherapy	CT	Both (empty for whole bladder treatment/full for SIB)	Bladder: 64 Gy (32f) SIB: 68 Gy	Iso (5 to 30 mm by 5 mm steps)	Both	21	– Better target coverage with 5–15 mm margins PTV
	Webster et al. (2013)	R	20	RTC3D	CT	Empty	Bladder: 52,5Gy (20f)	Aniso	Empty	Recognized but not specified	– Better coverage of CTV (V95%) – Mean irradiated volume reduced by 14,6 à 35%
	Murthy et al. (2016)	P	44	Tomotherapy	CT	Both (empty if whole bladder treatment/full if SIB)	Bladder: 64 Gy (32f) PLN: 55 Gy SIB: 68 Gy	Both	Both	Recognized but not specified	– Better locoregional control after 3 years – Reduction of grade 3 acute and late urinary toxicity
	Canlas et al. (2016)	R	8	N/A	CT	Empty	Bladder: 64 Gy (32f)	Aniso	Empty	Recognized but not specified	– Mean irradiated healthy volume tissue reduced by (95% of prescribed dose)
	Murthy et al. (2019)	R	106	RCMI	CT	Full	Bladder: 64 Gy (32f) PLN: 55 Gy SIB: 68 Gy	Aniso	Full	N/A	– Acceptable toxicity (7,5% for grade 3–4 acute GU)

(*continued on next page*)

Table 3 (*continued*)

ART strategy	Reference	Type of study	No. patients	Radiotherapy technique	Number of scanners for ART (CT/CBCT)	Bladder repletion during CT planning	Volumes and prescription doses (number of fractions)	Iso or anisotropic margins	Bladder repletion during treatment	Additional time (min)	Observed benefit
PoD individualised based on CBCT	Wright et al. (2010)	R	2	RCMI	CT + 4 CBCT	Empty	Bladder: 60 Gy (30f) SIB: 70 Gy	Aniso	N/A	N/A	– Better local control with SIB
	Vestergaard et al. (2010)	R	10	RCMI	CT + 5 CBCT	Empty	Bladder: 60 Gy (30f)	Aniso	Empty	N/A	– Mean volume receiving 95% of prescribed dose reduced by 30 to 40%
	Kron et al. (2010)	P	27	RTC3D	CT + 5 CBCT	Empty	Bladder: 64 Gy (32f)	Iso (5 mm)	N/A	N/A	– Lower integral dose due to more conformal irradiation despite the dose of IGRT
	Tolan et al. (2011)	P	11	RCMI	CT + 15 CBCT	Full	Bladder: 60–66 Gy (30-32f) PLN: 40–46 Gy	Iso (5 mm)	Full	N/A	– Mean irradiated volume reduced by half
	Foroudi et al. (2011)	P	27	RTC3D	CT + 5 CBCT	Empty	Bladder: 64 Gy (32f)	Iso (5 mm)	Empty	11	– Reduction of small bowel V45Gy and V5Gy by 29% and 15% – Similar coverage
	Kuyumcian et al. (2012)	P	27	RTC3D	CT + 5 CBCT	Empty	Bladder: 64 Gy (32f)	Iso (5 mm)	Empty	Recognized but not specified	– Better distribution in selection plans (PTVsmall and large)
	Vestergaard et al. (2014)	R	13	VMAT	CT + 4 CBCT	Empty	Bladder: 60 Gy (30f) SIB: 70 Gy	Aniso	Empty	N/A	– Mean healthy volume tissue irradiated reduced by 36% with DVF-ART technique
	Vestergaard et al. (2014)	P	20	VMAT	CT + 4 CBCT	Empty	Bladder: 60 Gy (30f) PLN: 48 Gy	Iso (5 mm)	Empty	8	– Mean healthy volume tissue irradiated reduced by 183 cm3 on average (30%)
	Foroudi et al. (2014)	P	50	RTC3D	CT + 5 CBCT	Empty	Bladder: 64 Gy (32f)	Iso (7 mm)	Empty	Recognized but not specified	– Poor daily CTV coverage in 18% of cases
	Gronborg et al. (2015)	P	9	VMAT	CT + 4 CBCT	Empty	Bladder: 60 Gy (30f)	Iso (5 mm)	Empty	Recognized but not specified	– Mean irradiated volume of small bowel reduced by 113 cm3
	Tuomikoski et al. (2015)	R	10	RCMI	1 CT + 4 CBCT (RepeatCBCT) 4 CT 15 min apart (RepeatCT)	Both	Bladder: 60 Gy (30f)	Aniso	Empty	N/A	– PTV volume reduced by 46% with CT-repeat method and 36% with CBCT-repeat
PoD individualized based on repeat CT	Tuomikoski et al. (2011)	P	5	VMAT	4–5 CT (15 min apart after voiding + drinking)	Both	Bladder: 45–50.4 Gy (25-28f) SIB: 55.8–65 Gy	Aniso	Empty	5–10	– Mean irradiated volume of small bowel reduced by 155 cm3 on average – Risk of grade 2 acute toxicity reduced by 35 to 7%
	Lalondrelle et al. (2011)	P A-POLO	15	RTC3D	3 CT (T0, T15 and T30)	Empty, medium and full	Bladder: 36 Gy (6f)	Iso (15 mm)	Empty	15–20	– Better PTV coverage (V95% >95%), by 51% to 96%
	Meijer et al. (2012)	P	20	RCMI	2 CT (empty and full)	Full	Bladder: 46 Gy (23f) SIB: 59.8 Gy	Iso	Full	12	– Reduction of dose to small bowel – No grade 3 toxicity
	Tuomikoski et al. (2013)	P	5	VMAT	4 CT (empty then filling)	Both	Partial bladder: 52,5Gy (21f)	Both (iso for 3 patients and aniso for 2)	Empty	N/A	– Reduction of dose to small bowel

Table 3 (*continued*)

ART strategy	Reference	Type of study	No. patients	Radiotherapy technique	Number of scanners for ART (CT/CBCT)	Bladder repletion during CT planning	Volumes and prescription doses (number of fractions)	Iso or anisotropic margins	Bladder repletion during treatment	Additional time (min)	Observed benefit
							or Whole bladder: 44 Gy (22f) + SIB: 64 Gy				– No significant difference in target coverage
	Hutton et al. (2013)	R A-POLO	10	N/A	2 CT (T0 and T30 after voiding + drinking)	Both	Bladder: 55 Gy (20f)	Aniso	Empty	4	– Additional time of 4 min per fraction in case of ART
	McDonald et al. (2013)	P A-POLO	25	RTC3D	2 CT (T0 and T30 after voiding + drinking)	Both	Bladder: 36 Gy (6f)	Aniso	Empty	14	– Mean healthy volume tissue irradiated reduced by 219 cm3 on average – Frequency of PTV selected "small" and "medium" of 49% and 45% respectively
	Lutkenhaus et al. (2015)	P	10	VMAT	2 CT	Both	Bladder and PLN: 40 Gy (20f)SIB: 55–60 Gy	Iso (7 mm/9 mm if SIB)	Full	Recognized but not specified	– Better pelvic lymph nodes coverage (V95%>99%) – Significant reduction of bowel volume receiving 30 Gy and 40 Gy
	Tuomikoski et al. (2015)	R	10	RCMI	1 CT + 4 CBCT (RepeatCBCT) 4 CT 15 min intervals (RepeatCT)	Both	Bladder: 60 Gy (30f)	Aniso	Empty	N/A	– Greater PTV volume reduction by CT-based POD (46%) than CT–CBCT-based POD (36%)
	Hafeez et al. (2016)	P A-POLO	18	RCMI	2 CT (T30 and T60 after voiding + drinking)	Full (2 filling times)	Bladder: 52 Gy (32f) SIB: 70 Gy (32f)	Aniso	Full (voiding + drinking 30 min before treatment)	13	– Respectively 97.07+/-2.10% and 99.97+/-2.62% for mean D98 PTV SIB and whole bladder – No more toxicity with dose escalation
	Hafeez et al. (2017)	P A-POLO	55	RTC3D	CT	Full	Bladder: 36 Gy (6f)	N/A	Full	N/A	– Local control: 92% – Acceptable grade 3 toxicity (18% for GU and 4% for GI)
Re-Opt and PoD	Vestergaard et al. (2013)	R	7	RCMI	CT + 5 CBCT (PoD) Daily CBCT (Re-Opt)	Empty	Bladder: 60 Gy (30f)	Iso (3 mm for PoD/5 mm for Re-Opt)	Empty	N/A	– Reduction in the healthy volume tissue receiving 95% of prescribed dose by 66% for PoD and 41% for Re-Opt
	Kong et al. (2018)	R	10	RCMI	1 CT (non indiv PoD) 1 CT + 5 CBCT (PoD indiv) Daily CBCT (Re-Opt)	Full	Bladder: 46 Gy (23f)	Iso (0, 5, 10 and 15 mm for PoD non indiv/5 mm for PoD indiv and Re-Opt	Full	N/A	– Reduction in the volume of healthy irradiated tissue by 25% (Re-Opt), 16% (PoD indiv) and 12% (non indiv PoD) versus conventional treatment

Art: Adaptive Radiotherapy; CBCT: Cone Beam Computed Tomography; PoD: Plan Of the Day.

sisting for 4–6 weeks after TURBT, MRI should be performed as far as possible from the TURBT, accounting for the need to start RT 4–8 weeks following TURBT.

However, due to insufficient data on the role of mp-MRI to optimize the management of MIBC and more specifically bladder RT, we cannot make strong recommendation on its use [37]. Therefore, in both cases discussed above, bladder mp-MRI can be recommended only if the waiting period for the examination does not delay patient management.

Delineation of the target volumes

Gross tumor volume (GTV)

The GTV refers to any residual gross disease following TURBT, visualized on cystoscopy or on a contrast-enhanced CT or MRI scan.

Ideally, no GTV should be delineated as TURBT should be complete, but situations exist when TURBT cannot be complete, especially when the tumor extends outside the wall of the bladder. In these cases, a GTV can be delineated using geographic information from: cystoscopy, contrast-enhanced planning-CT, imaging before or after TURBT (CT or MRI). If a GTV needs to be delineated, pre- and/or post-TURBT MRI, when available, should be fused with the planning CT (T2 weighted images).

Clinical tumor volumes (CTV)

General considerations. The tumor CTV is usually the whole bladder contoured as a solid organ, with inclusion of any extravesical tumor spread. The rationale for including the whole bladder is the multifocality of lesions both at presentation and at recurrence [38], although partial bladder irradiation has been assessed in trials and will be discussed in this article. The question as to whether an additional CTV margin should be applied beyond the bladder wall to take into account the microscopic extravesical extension is not consensual. In a retrospective series of radical cystectomy correlating pre-operative imaging and definitive pathology, Jenkins et al. estimate that the overall accuracy of CT scans to predict extravesical extension is 44%, with understaging being more frequent than overstaging. The 90th percentiles of the maximum extravesical extension on histological specimen were 9.6 mm among patients with extravesical extension seen on pre-operative CT, and 6.3 mm among patients with organ-confined disease on CT. Squamous differentiation, lymphovascular invasion and tumor size >35 mm were correlated with the extent of extravesical extension [39].

Extravesical extension can also be directly assessed on the bladder mp-MRI, if performed.

Partial bladder irradiation versus whole bladder irradiation. Partial bladder irradiation has been evaluated in an RCT [40]: 149 patients with T2T3N0 MIBC were randomized between whole bladder irradiation (52.5 Gy in 20 fractions) versus dose-escalated partial bladder irradiation of the index lesion (57.5 Gy in 20 fractions or 55 Gy in 16 fractions), without chemotherapy in both arms. The authors hypothesized an improvement in 5-year local control with dose-escalated partial bladder irradiation. Partial bladder irradiation resulted in a 61% reduction in the median irradiated bladder volume compared to the whole bladder arm, and allowed the delivery of an increased radiation dose without increased toxicity. However, this superiority study was negative as the experimental armit failed to show an improvement in local control or OS, and therefore, partial bladder irradiation (with or without dose-escalation to the tumor index) cannot be recommended outside of a clinical trial.

Inclusion of proximal urethra/prostate/vagina anterior wall. Among males with MIBC, occult pathological prostatic involvement has been found in 24–43% of cystoprostatectomy specimens: the pattern of involvement was mainly non-contiguous via in situ spread within prostatic urethra/ducts epithelium and more rarely contiguous via transmural invasion [41–45]. Among patients with prostatic involvement, stromal involvement occurred in 37–75% [41,44–46]. Three main risk factors of prostatic involvement have been identified: presence of CIS, multifocal disease and trigone/bladder neck involvement [43,47]. In these cases, the inclusion of the whole prostate (with no additional margin) in the CTV can be discussed.

Among females, proximal urethral involvement occurs in approximately 12% of patients, the only risk factor being bladder neck or anterior vaginal wall invasion [48,49]. Microscopic vaginal and cervical involvement remain rare (around 5%), and in most cases are associated with urethral involvement. This was correlated with stages T3b and T4 disease in a series of 115 women who underwent radical cystectomy [49]. Therefore, in case of bladder neck involvement and/or anterior vaginal wall involvement, the inclusion of proximal urethra (until pelvic floor) can be discussed in the CTV, with no additional margin. To delineate proximal urethra, an MRI is recommended. Due to the rarity of infraclinic vaginal involvement, anterior vaginal wall should not be routinely included in the CTV in the absence of visible invasion.

Index tumor clinical tumor volume. As well as the standard CTV, an index tumor CTV has been described which classically encompasses the tumor bed +/− any residual gross tumor with no additional margin for microscopic extension [40,50–52]. This index tumor CTV can be utilized in two situations:

- partial bladder irradiation (although partial irradiation is not recommended);
- or when a two dose level approach is considered: either for index tumor dose escalation (with standard dose to the whole bladder) or for whole bladder dose de-escalation (with standard dose to the index tumor).

The definition of an index tumor CTV should be limited to the following cases:

- no multifocal lesions and/or no CIS away from the index tumor: the multifocality of CIS can be assessed by hexaminolevulinate photodynamic diagnosis-assisted TURBT, with systematic biopsies of suspicious areas on blue light examination, while randomized biopsies of optically healthy mucosae are usually not recommended [53];
- index tumor easily identifiable: either due to a macroscopic residual lesion following incomplete TURBT (i.e. GTV), or due to the presence of gold fiducial markers set during the TURBT with good consistency with the pre-TURBT imaging (contrast-enhanced CT or MRI) and the planning CT;
- index lesion located outside the dome (due to the risk of geographical miss during dose delivery) and ideally upon the trigone;
- ratio of index tumor CTV upon whole bladder <25% approximately, to allow a significant sparing of the rest of the bladder.

Two strategies performed during TURBT have been suggested to help identify the index tumor for delineation or image-guidance purposes [54]:

- insertion of 3–4 gold fiducial markers near the tumor bed [55] (although concerns about motion of the fiducial exist due to bladder filling) [54];

Table 4
Summary of guidelines from the working group for bladder radical radiotherapy.

Topics	Proposition of guidelines	Evidence strength	Grade of recommendation
1. TURBT preceding radiotherapy	A complete TURBT must be performed within 4–8 weeks before the start of radiotherapy.	A	1
	When TURBT has been performed more than 6 weeks before the start of RT, a second look should be performed to ensure that there is no tumor regrowth.	B	2
2. Planning CT-scan acquisition	When standard planning is performed (i.e. without adaptive strategy): – if single-dose level whole bladder radiotherapy is planned, patients have to stop any absorption of fluids within 30 minutes before the planning CT and to void bladder immediately before planning CT. – when index tumor irradiation is planned, patients have to void bladder then drink 250–500 ml of water approximately 30 minutes before the planning CT.	B	2
	Ideally, rectum should be empty as well, with the same local practices as those used for prostate planning.	C	2
	Patients must be supine in comfortable position with adequate immobilization devices (knee and/or ankle supports).	C	1
	CT scan thickness should be $\leq$3 mm; the superior limit must be at the L3/L4 level (to encompass common iliac vessels), and the inferior limit must be 2 cm below ischial tuberosities.	C	1
	CT should be contrast-enhanced if renal function allows it, only in cases of: extravesicular extension at diagnosis, incomplete TURBT, delay of more than 6 weeks between the TURBT and the planning CT with no second look feasible before starting, or in case of pelvic lymph nodes (PLN) irradiation.	C	No consensus
4. Bladder MRI	–		
3. Delineation of target volumes			
– GTV	Ideally, no GTV should be delineated as TURBT must be complete, but situations exist when TURBT cannot be complete, especially when tumor extends outside the wall of the bladder. In these cases, a GTV will be delineated using geographic information from: cystoscopy, contrast-enhanced planning-CT, imaging before or after TURBT (CT or MRI). Post-TURBT contrast-enhancement should be considered cautiously due to the frequent post-resection scarce.	C	1
– CTV	Whole bladder irradiation should be privileged.	A	1
	Standard CTV should encompass the whole bladder as a solid organ with inclusion of any residual gross lesion.	A	1
	We do not recommend systematic circumferential margin for CTV delineation.A margin should recommended: – if the index tumor is identifiable, an additional margin outside the bladder wall should be added regarding the lesion only: of 6 mm in case of no visible extra-vesicular extension, and of 10 mm in case of visible extra-vesicular extension (+/- in case of tumor > 35 mm, squamous differentiation or lymphovascular invasion). – if the index tumor is not identifiable, no additional margin should be added.	B	2
	Among males : – in case of clinical prostatic involvement, the whole prostate should be included in the CTV; – in the cases of CIS and/or multifocal lesions and/or trigone/bladder neck involvement, but with no clinical prostatic involvement, inclusion of the whole prostate in the CTV is optional;	B	2
	Among females : – the inclusion of proximal urethra (until the pelvic floor) in the cases of bladder neck and/or anterior vaginal wall involvement is optional; – anterior vaginal wall should not be routinely included in the CTV in the absence of visible invasion	B	2
	An index tumor CTV can be delineated in addition to the standard CTV when a bladder two-dose level approach is considered; it corresponds to the tumor bed and any residual GTV identified with the aid of imaging, cystoscopic data and if possible markers set following TURBT, with no additional margin.	B	2
– PTV	We recommend anisotropic CTV-to-PTV margins.	B	1
	Within a non-adaptive strategy, when bony alignment only is used, CTV-to-PTV margins should be of 1.5 to 2 cm in all directions except for superior and anterior directions where margins of 2 to 2.5 cm should be used.When a daily soft-tissue imaging realignment IGRT (such as CBCT) is used, it is reasonable to reduce these anisotropic margins to 1 to 1.5 cm and 1.5 to 2 cm, respectively.	B	1
	Margins should not differ between empty bladder and full bladder protocols.	B	No consensus
	When PTV margins are applied on the index tumor CTV, daily soft tissue imaging should be systematically performed, and margins should take into account the localization of the tumor within the bladder: we recommend at least 1.5–2 cm in all directions for tumor of the superior wall or the anterior wall, and 1–1.5 cm in all directions in the other cases.	B	2
4. Radiotherapy regimen			
– Dose/fractionation	Continuous course chemoradiotherapy should be privileged, especially with >T2 tumors.	B	1
	Conventional fractionation or moderate accelerated hypofractionation are both relevant schedules for continuous schedules, with respective prescribed doses to the whole bladder of 64 Gy in 32 fractions, or 50–55 Gy in 20 fractions.	A	1

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Table 4 (*continued*)

Topics	Proposition of guidelines	Evidence strength	Grade of recommendation
	When split-course schedule is chosen, the RT regimens should be in accordance to the MGH/RTOG protocols, with two courses of accelerated hypofractionated RT (induction then consolidation according to response), in order to avoid any extended overall treatment time, leading to an overall pure hyperfractionated regimen.	A	1
– Dose escalation(innovative approach to be assessed in clinical trials)	Dose escalation to index tumor is not recommended routinely, and should be reserved for solitary tumors with no CIS away from the index tumor; the site of the index tumor should be easily identifiable and should be outside the dome (ideally upon the trigone), with a ratio of index tumor CTV/whole bladder CTV <25%.	B	2
	If dose escalation is performed: a simultaneous integrated boost approach is encouraged, within a conventional fractionation schedule to the whole bladder, to a total escalated dose of 68 Gy in 32 fractions	C	2
	If dose escalation is performed: adaptive-radiotherapy should be used, with associated dedicated repletion guidelines	B	2
	In the absence of adaptive radiotherapy planning, the patient should have comfortably full bladder for planning CT and treatment.	B	2
– PLN radiotherapy	PLN radiotherapy is not recommended routinely.	B	No consensus
	If performed: one can consider either small pelvic CTV or extended pelvic CTV, with usual vessels based delineation guidelines.	B	No consensus
	If performed: it should be integrated only within a conventional fractionated schedule with simultaneous integrated boost, to a dose of 51.2–54.4 Gy in 32 fractions of 1.6–1.7 Gy.	C	2
5. Radiotherapy delivery			
– IMRT/IGRT	Radiotherapy for bladder cancer should be performed using both IMRT and IGRT based on soft-tissue imaging.	B	1
– Adaptive radiotherapy (innovative approach to be assessed in clinical trials)	Although no clinical benefit has been shown yet, adaptive radiotherapy should be privileged when possible, especially when a dose-escalation boost is performed.	C	2
	Among the different approaches, the optimal balance between dosimetric benefits and logistical/technical requirements seems to be a PoD approach, either non individualized or individualized with repeat CT, preferentially using the A-POLO approach.	B	2
	PoD strategies should be used with no more than 3 different plans	B	2
	PoD strategies should be implemented within a training program to improve the daily plan selection process.	B	2
6. Concurrent systemic treatment	Concurrent systemic treatment (either chemotherapy or hypoxia modification) should be associated to radical RT for patients whether or not they are eligible for cisplatin.	A	1

GTV = Gross Tumor Volume; CTV = Clinical Target Volume; PTV = Planning Target Volume; IMRT = Intensity Modulated RT; IGRT = Image Guided RT; TURBT = Transurethral Resection of Bladder Tumor; EQD2Gy = equivalent dose in 2-Gy fraction; PoD = Plan of the day; A-POLO = adaptive predictive organ localization.
Evidence strength: A – high quality evidence (well-conducted randomized clinical trials (RCTs), exceptionally strong observational studies); B – moderate quality evidence (RCTs with some weaknesses, generally strong observational studies); C – low quality evidence (observational studies that provide conflicting information or design problems (such as very small sample size)).
Grade of recommendation: strong (1), moderate (2) or weak (3).

- tumor demarcation using sub-urothelial injection of lipiodol through a flexible cystoscope [56].

However, these strategies are still under investigation and should not be considered as a standard of care.

Pelvic lymph node clinical tumor volume. Pelvic lymph node (PLN) CTV definition is discussed along with potential indications of PLN irradiation in section 3.5.5.

Planning target volume (PTV)

CTV to PTV margins take into account set-up margins as well as internal motions relating to changes of position, volume and shape of the organ, both between each fraction (inter-fraction) and within a fraction (intra-fraction).

Inter-fraction motion. Inter-fraction motions of the bladder wall are complex, essentially depending on bladder and rectum filling [57–59], with maximal shifts above 2 cm within the whole course of radiotherapy. This motion is anisotropic as superior and anterior bladder portions have greater amplitudes of motion [60–63]. Changes in bladder volumes relative to the planned CTV have been widely described over the treatment and showed a weekly variation around 20–30%, mainly towards a decrease [31,63,64]. However, some series have concluded an unpredictable pattern of volume variations, with cases of both larger and smaller bladders in the same patient over the course of radiotherapy [65].

Interestingly, Lotz et al. have assessed the variations in both GTV shape and position during a course of radiotherapy, estimating that variations in GTV shape were small compared to GTV translations (standard deviation of the GTV center of gravity 0.1–0.9 cm). Translations were largest in the cranio-caudal and antero-posterior directions, and were strongly correlated with the tumor location on the bladder wall (larger for tumors at the cranial and the anterior parts of the bladder) [58].

Intra-fraction motions. Intra-fraction motions have been studied by repeated pre-treatment and post-treatment soft-tissue imaging, or by cine-MRI. Among 15 patients receiving 80 fractions, Lalondrelle et al. estimated using pre- and post-treatment cone beam CT (CBCT) that the bladder volume changed by 9 cc (SD 16 cc, range 32–52 cc) over a fraction (with a mean time of 13 min). This was associated with bladder wall translations, predominantly in cranial (mean 2.4 mm) and anterior direction (mean 2 mm) [65]. Mangar et al. assessed intra-fraction bladder motion using cine-MRI in nine patients. An increase in volume of 1.6 cm^3 per minute was

observed during a fraction, corresponding to a bladder volume increase of 30%. For volumes up to 150 cc, this bladder filling was linearly correlated with a displacement of the superior, inferior and anterior bladder walls [66].

Motion according to bladder filling. The correlation of inter- and intra-fraction motions and bladder-filling protocols was investigated by Dees-Ribbers et al. Among 24 patients with pre and post-treatment CBCT, eight patients were treated with an empty bladder and sixteen with a full bladder. Both protocols showed similar intra- and inter-fraction motions, with largest movement in the cranial and anterior directions in both cases [30]. On the contrary, Pos et al. found that a large bladder volume and rectal diameter at planning CT was predictive of a large volume variation and a large tumor spatial variability [31].

Planning target volume margins (without adaptive strategies). CTV to PTV margins should be chosen to ensure that the CTV is covered in most of the fractions and ideally by the 95% isodose line [67]. This global margin is highly dependent on the daily alignment method applied. Empirically, population-based CTV to PTV margins of 2 cm or more have been proposed, before the use of IGRT with soft tissue imaging realignment [68].

Adapted margins have been proposed according to alignment method with two main strategies. First, several series assessed the percentage of patients for whom a given proportion of the wall displacements is covered by a margin from the CTV [31,69–71]. For example, Foroudi et al. estimated that bladder CTV coverage with a margin of 0.5, 1.0, 1.5, 2.0 and 2.5 cm was 0%, 19%, 56%, 93% and 96%, respectively based upon daily skin alignment. CTV coverage was 0%, 41%, 63%, 89% and 96% respectively, based upon daily bony alignment. It was 52%, 89%, 96%, 100% and 100%, respectively based upon daily soft-tissue alignment. Interestingly, with soft-tissue alignment, the overall insufficient coverage of CTV with a 1 cm margin is linked to insufficient coverage in the anterior and posterior directions in 90% of cases [69]. Another strategy to determine CTV to PTV margin is to assess, for each direction, and for a population of patients, uncertainties on systematic errors (Σ) and on random errors (σ) for each component (organ motion and set-up) of a given alignment method, as compared to a gold standard and to apply "Van Herk-like" recipes [64,67,72]. The more precise the alignment method, the more the uncertainties on Σ and σ will decrease, and the more the CTV to PTV margin can decrease. Based on portal imaging alignment methods, Meijer et al. estimated that CTV to PTV margins should be 1 cm laterally and anteriorly, 1.2 cm caudally, 1.4 cm posteriorly and 2 cm cranially [72]. However, these recipes have been described for translation motions mainly, and therefore are not perfectly adapted to bladder motion which contains shape and volume modifications as well.

Organs at risk

The delineation of organs at risk should follow standard practices, for bowel bag, rectum, anal canal and femoral heads [73].

Radiotherapy regimen

The regimens and clinical outcomes are summarized in Tables 1 and 2.

Conventional fractionation

A radiotherapy dose–response effect has been suggested in several series [74,75]. For example, Pos et al. estimated that an increase in total dose of 10 Gy was associated with a 1.44-fold increase in the 3-year local control [75]. In trimodal therapy prospective trials using conventional fractionation and no dose-escalation, the total prescribed dose to whole bladder was then relatively concordant, ranging from:

- 60–64 Gy when homogeneous dose was prescribed to the whole bladder [10,76–81];
- 39.6–52 Gy when a two-dose level irradiation was prescribed, with total dose to the index tumor ranging from 54 Gy to 65 Gy [22,28,78,82–88].

The overall treatment time (OTT) ranged from 6 weeks (for continuous schedule) to 9 weeks (for split course schedules).

In one study assessing dose escalation to the index tumor, total dose was 64 Gy on the whole bladder and 68 Gy on the index tumor [89].

Altered fractionation

When delivering radiotherapy, fractionation refers to two linked parameters, the dose per fraction and the OTT; altered fractionation therefore implies modification of one or of these two parameters, as compared to the conventional fractionation. A decrease of OTT (less than 6 weeks) typically aims to avoid clonogenic tumor repopulation (for tumors with high α/β ratio), with potential benefits on quality of life and cost-effectiveness, at the cost of increased acute toxicity; while a decrease of dose per fraction aims at reducing late toxicity [90].

OTT for the bladder has been suggested to have an impact on outcome as tumor clonogenic repopulation in urothelial carcinoma of the bladder was shown to accelerate after a lag period of about 5–6 weeks following the start of treatment. It was thus concluded that a dose increment of 0.36 Gy per day was required to compensate for this repopulation [91]. Similarly, the α/β ratio higher than 10 Gy [92] suggests a low sensitivity to fractionation for urothelial bladder cancer cells.

Pure hyperfractionated radiotherapy (without acceleration). Pure hyperfractionated radiotherapy refers to a regimen with OTT of at least 6 weeks, and dose per fraction <1.8 Gy. Several bladder-sparing prospective trials (from the Boston "2nd and 3rd generation" studies) can be considered as pure hyperfractionated regimens [24–26,28,29]. Indeed, they included bi-fractionated regimens (2 fractions per day), with dose per fraction of around 1.5 Gy, and OTT of 8–9 weeks due to a split-course schedule. Zapatero et al. used the same schedule [93]. In these trials total dose to the bladder ranged from 45.6 Gy to 52.3 Gy and total dose to the index tumor was 64.3–64.8 Gy. Hafeez et al. reported results of a dose-escalation regimen using pure hyperfractionated radiotherapy on the whole bladder and moderate accelerated boost on the index tumor with acceptable oncological outcomes and tolerance [94].

Pure hypofractionated radiotherapy (without acceleration). Two trials report on the outcome of a bifractionated (BID) hypofractionated protracted regimen (OTT = 11.5 weeks) with split course among patients with localized operable MIBC: 3 Gy b.i.d at days 1, 3, 15, 17 on the whole pelvis followed by reevaluation, then, in case of complete response, 2.5 Gy b.i.d at days 64, 66, 78, 80, to a total dose of 44 Gy on the whole bladder. Complete response was obtained in 67 to 74%, and 3-year OS was 59% to 83% [23,95].

Hyperfractionated accelerated radiotherapy. The phase II EORTC 22971 trial is the only prospective trimodal therapy assessing hyperfractionated accelerated radiotherapy (2 daily fractions of 1.2 Gy up to 60 Gy on the whole bladder over 5 weeks). However, only 9 patients were enrolled and therefore, this study is not discussed here [96].

Hypofractionated accelerated radiotherapy. Moderate hypofractionated accelerated radiotherapy has been assessed in five trimodal therapy trials (including one trial using non-chemotherapy based radiosensitizers) [76,79,97–99]. Radiotherapy was delivered continuously over 4 weeks on the whole bladder to a total dose of 52.5–55 Gy. No direct comparison of hypofractionated versus conventional fractionated radiotherapy for trimodal therapy exists to date; however an individual patient-data meta-analysis of two phase III randomized trials [76,79] was recently published comparing two schedules widely used in the UK: 64 Gy in 32 fractions and 55 Gy in 20 fractions among 782 patients. While the toxicity profile was similar between the two regimens, the hypofractionated schedule was non-inferior to a conventionally fractionated schedule in terms of invasive locoregional recurrence (ILRC) and OS, and superiority of the hypofractionated schedule was demonstrated for ILRC (adjusted HR 0.71 [95% CI 0.52–0.96]) [100].

Dose-escalated tumor boost

Dose to the index tumor can be regarded as escalated if the equivalent dose in 2 Gy fraction (EQD2Gy) is more than 66 Gy. The rationale to propose such escalated doses refers to the pattern of recurrence following radiotherapy mostly at the original primary bladder tumor site [101] and to the radiation dose–response effect in urothelial bladder cancer [74,75].

Several retrospective studies have reported interesting results using intensity modulated radiotherapy (IMRT) with simultaneous integrated boost, with various schedules [51,102].

Three trimodal therapy prospective trials have assessed high dose tumor boost delivered with image-guided adaptive radiotherapy. Following a pilot feasibility study of ten patients [103], Murthy et al. prospectively assessed the clinical outcome of 44 patients with localized MIBC treated with conventional fractionated radiotherapy to the whole bladder (64 Gy/2Gy) and weekly cisplatin [89]. Patients with a solitary tumor or 2 tumors in close proximity and without CIS were deemed suitable for dose-escalation using a simultaneous integrated boost to the tumor bed to a dose of 68 Gy/2.125 Gy (EQD2Gy = 68.7 Gy); 55% received the escalated dose. Adaptive radiotherapy was used (Tables 1 and 2). While OS and locoregional control rates were better among patients receiving the escalated dose, it was not statistically significant.

Similarly, Hafeez et al. prospectively assessed trimodal therapy with image-guided adaptive radiotherapy using an high dose simultaneous integrated boost to the index tumor: 52 Gy/32 fractions to the whole bladder and 70 Gy/32 fractions to the tumor bed (EQD2Gy = 71 Gy) [94]. Eighteen out of 20 patients completed treatment to 70 Gy; 17 patients were alive and disease-free at a median follow up of 19 months, and no muscle-invasive recurrence occurred. No late grade $\geq$3 gastro-intestinal toxicity was observed and two patients experienced late grade $\geq$3 genito-urinary toxicity. Planning CT for simultaneous integrated boost irradiation in both trials was performed with comfortably full bladder protocols [89,94].

This treatment approach is currently being assessed in a randomized phase II trial (RAIDER) comparing adaptive image guided standard dose versus escalated dose radiotherapy (NCT02447549).

Split course versus continuous schedule

When given as an alternative to surgery for patients unfit for surgery and/or with inoperable tumor, continuous chemoradiotherapy is routine as salvage-cystectomy is not feasible.

When given as trimodal therapy with the aim of bladder-sparing for resectable tumors and fit patients, two strategies have been proposed. In protocols used in the RTOG trials, candidates for bladder-sparing were selected according to their early response to induction chemoradiation; only those with complete (or near complete) pathologic response could pursue with consolidation chemoradiation, while non-responder patients were referred for early cystectomy [6]. This implies a gap of 3–5 weeks during the course of chemoradiotherapy (split course), between induction and consolidation chemoradiotherapy. Conversely, protocols developed at the University of Erlangen consist of an up-front full-course of chemoradiotherapy with no interruption and with early evaluation (at around 6 weeks after the end of radiotherapy), with potential salvage-cystectomy according to response [104].

No formal comparison exists between the two approaches and concerns have been raised about increased OTT with split course due to radiobiological reasons. Overall, prospective split course trimodal therapy protocols have been designed with conventional fractionated radiotherapy [10,28,29,77,82,83,85,86,88], pure hyperfractionated radiotherapy [24–26,28,29,93] and pure hypofractionated radiotherapy [23,95]. In the two latter cases, split protocols consisted of two accelerated courses of chemoradiation (induction and consolidation) separated by a break. Prospective continuous trimodal therapy protocols have been designed with conventional fractionated radiotherapy [76,78–81,84,87,89], pure hyperfractionated radiotherapy [94] and hypofractionated accelerated radiotherapy [76,79,97–99] (Tables 1 and 2).

In a meta-analysis of trimodal therapy studies, Arcangeli et al. found that the complete response rate was significantly better in patients treated with a continuous schedule compared to split course (HR = 0.513, (95%CI 0.430–0.611)). This was confirmed as an independent prognostic factor in multivariable analysis. Consequently, salvage cystectomy was more frequent with split course (25% vs 19%), $P < 0.05$). However, the early reevaluation of split course should be kept in mind after induction chemoradiotherapy, so a low radiation dose level delivered may potentially lead to inappropriate, premature salvage cystectomy, while it is performed after full-course treatment in the continuous schedule. No differences were found in bladder-intact survival or 5-year OS. In subgroup analysis, 5-year OS was significantly better with a continuous course compared to split course among patients with >T2 tumor stage (HR = 0.641, 95%CI = 0.424–0.969), while there was no difference in complete response rate [105].

Pelvic lymph nodes (PLN) irradiation

PLN irradiation among patients with cN0 bladder cancer is an important matter of debate. The rationale to propose PLN irradiation is multiple: radical cystectomy with PLN dissection series in cN0 patients showing PLN micrometastases in around 25% [106,107], the important rate of pelvic recurrences following radical cystectomies and PLN dissection, and the negative impact of no or limited pelvic lymph nodes dissection on these recurrences [108].

Most trimodal therapy trials initially incorporated PLN (either small pelvis (upper limit S1–S2 or S2–S3) or standard pelvis (upper limit L5-S1)). Dose to the pelvis ranged from 36 Gy to 55 Gy in conventional fractionated radiotherapy [10,22,28,77,80–89], and was of 44.8–45.6 Gy in pure hyperfractionated radiotherapy [24–26,28,29]. PLNRT was not performed in trimodal therapy hypofractionated protocols (Tables 1 and 2).

One phase III randomized controlled trial assessed the benefit of PLN radiotherapy: 230 patients with T2–T4, N0 urothelial bladder cancer were randomized between whole-pelvis (WP) and bladder-only (BO) continuous conventional fractionated chemoradiotherapy (with weekly cisplatin) following TURBT [87]. In both arms, dose to the whole bladder was 45 Gy and dose to the index tumor was 65 Gy: dose to the pelvis in the whole pelvis arm was 45 Gy. The primary endpoint was highly composite as it comprised toxicity, locoregional control, distant control, disease-free survival and OS. With a median follow-up of 5 years, there was no difference between whole pelvis and bladder only in late toxicity, loco-

regional recurrence (41% vs 43%), 5-year PFS (47% vs 47%) and 5-year OS (53% vs 51%). However, it is worth mentioning that an isotropic 2-cm margin from the bladder walls was used with 3D conformal planning and that the bladder filling protocol was not specified, as such, at least the internal iliac vessels likely received a significant radiation dose even in the bladder-only group. These data are in line with the low rate of pelvic recurrence (6%) following bladder-only radiotherapy in the randomized BC2001 trial [76].

Among 315 patients with cT1-T4N0 urothelial bladder cancer undergoing radical cystectomy with PLN dissection (median number of dissected nodes of 19), Goldsmith et al. found that 26% had occult positive lymph nodes with the following subsite distribution: perivesicular 3%, obturator 17%, internal or external iliac 15%, presacral 3% and common iliac as high as 12%; the rate of lymph node involvement did not vary by clinical T-stage. The only predictor of pathologic pelvic lymph node involvement in multivariable analysis was the presence of lymphovascular invasion (LVI) on preoperative biopsy (OR 3.74, $P < 0.001$). It was marginally associated with occult common iliac LN involvement (OR 2.307, $P = 0.056$). Finally, they estimated that the percentages of patients with muscle-invasive disease and biopsy LVI, whose occult lymph nodes regions would have been fully encompassed by whole bladder CTV, small pelvic CTV and extended pelvic CTV (including common iliac nodes) were: 45%, 71% and 95%, respectively [107].

Lastly, the pelvic fields used in the trimodal therapy trials (Table 1) as well as contouring guidelines for adjuvant radiotherapy following radical cystectomy [109], suggest a standard upper limit in L5-S1 for PLN radiotherapy. However, the previous analysis of pattern of occult lymph node regions among MIBC [107] could prompt to include common iliac nodes as well. In all cases, usual delineation guidelines around the vessels for PLN CTV should be followed [110].

Radiotherapy delivery

Intensity modulated radiotherapy

While IMRT has been widely validated in prostate cancer [111] and gynecological cancers [112], few data are available in bladder cancer. Several retrospective studies have compared IMRT versus 3D conformal radiotherapy: overall, IMRT dose delivery was associated with improvement of rectum and bowel sparing [113,114], translating into less toxicity [113,115,116].

IMRT seems particularly relevant for hypofractionated schedules. In a retrospective series among elderly patients, hypofractionated IMRT (50 Gy in 20 fractions) within trimodal therapy was associated with 3-year OS and disease-specific survival of 61% and 71%, respectively, with no grade $\geq$3 late gastro-intestinal nor genito-urinary toxicity [117]. The other advantage of IMRT over 3D CRT could be the feasibility of simultaneous concomitant boost on the bladder or on the tumor, which is particularly useful with continuous radiation schedules [51,102].

Image guided radiotherapy (IGRT)

The assessment of bladder position and deformation relies on several imaging strategies [118]. In-room soft tissue imaging with either kilovoltage (kV) or megavoltage (MV) CBCT is the most frequent modality of IGRT enabling offline or online couch corrections. CBCT was used in several studies to define the optimal margins for planning (see section 2.3.3). While concerns about inter-observer variability of bladder boundary delineation on CBCT were suggested [119], the technical improvement of this IGRT modality has finally supported the wide applicability of CBCT in this field [120].

Ultrasound imaging is a non-irradiating imaging modality to assess and to monitor the bladder volume with strong correlations with CT findings [121], but with no control of bowel and rectum positions, and above all, no possibility to realign the isocenter. For these reasons, this modality is not routinely implemented for bladder radiotherapy. MR-guided radiotherapy is a promising IGRT strategy with high contract soft-tissue imaging, with availability to perform sagittal cine-MR [122].

Adaptive radiotherapy

Adaptive radiotherapy (ART) consists in the modification of dose distribution through a library of plans or re-planning once or several times over the course of the treatment. The objectives of ART are a better target volume coverage as well as better healthy tissue-sparing.

Several ART strategies for bladder radiotherapy can be distinguished. The modalities and benefits of the different strategies are summarized in Table 3. They have been described mainly within exclusive bladder radiotherapy (without PLN irradiation) studies.

Offline composite replanning strategy. This strategy uses the CBCT imaging acquired during the first week of treatment to create a new composite CTV/PTV representative of the target motions and deformations, and which will be used during the remaining fractions after re-planning [123–125]. This method takes into account mainly systematic deformations while random daily bladder changes are not well compensated.

Plan of the day strategies. Plan of the day (PoD) strategies are based upon the elaboration of several plans with the online selection of the optimal plan at each fraction, depending on the daily CBCT.

Non individualized plan of the day. Non individualized PoD strategies rely on the application of increasing population-based isotropic or anisotropic margins (generally in 5-mm increments) around the CTV from the planning CT to create several PTVs, leading to several treatment plans [89,102,103,125–129].

Individualized plan of the day. Two main methods have been described to create individualized PoD libraries. The first method requires a single post void planning CT and repeat daily CBCTs (usually from the first five fractions), to generate a patient-specific library of small, medium and large PTVs [61,127,130–139]. For example, Foroudi et al. determined the small CTV as the smallest of the six CTVs, the large CTV as the Boolean summation of all CTVs, and the medium CTV as the mean between the small and the large one, with finally a 5–7 mm uniform margin to create the corresponding PTVs [132,138].

The second method uses repeat planning CT (2 to 6) with different bladder filling conditions, from empty to full, to generate corresponding PTVs [65,94,137,140–146]. In the classical approach [137,140,143,144,146], index tumor CTV and bladder were either delineated on each different planning CT or only on the empty and full conditions, then extrapolated for the intermediate filling states. Finally, an isotropic margin of 5–7 mm around the bladder and of 9–10 mm around the GTV was added to account for residual errors, such as shape changes, delineation errors and intrafraction motion.

Another original method is referred to as the adaptive-predictive organ localization (A-POLO) [65,94,141,142,145]. This method relies on the modeling of an individual's pattern of bladder filling and organ displacement at treatment planning with the generation of a library of plans. The difference between the pre-treatment daily imaging and the actual delivery of radiotherapy, due to continuous filling in the meantime, will be assessed using the modeling information and positioning rearranged accordingly [66]. Globally, patients are asked to void their bladder and an immediately post-void CT is performed (CT0), then 30 min later

(CT30), with no voiding permitted between the scans [141]. Three PTV are generated from CTV delineated either on CT0 (CTV0) or CT30 (CTV30): PTV*small* and PTV*intermediate* are generated from CTV0 with margins of 0.5 cm (isotropic) and 1.5/1/0.5/1.5/0.5 cm in anterior/posterior/lateral/superior/inferior directions, respectively [65]. PTV*large* is generated according to the magnitude of bladder filling: if filling between CT0 and CT30 is over 50 cm^3, CTV30 is expanded of 1.5/1/0.5/1.5/0.5 cm in anterior/posterior/lateral/superior/inferior directions; otherwise, CTV0 is expanded of 2/1.2/0.75/2.5/0.75 cm in anterior/posterior/lateral/superior/inferior directions. Alternatively, Hafeez et al. asked the patients to drink 350 mL of water after voiding, and performed a CT at 30 min and 60 min, with the same cut-off of bladder filling (50 cm^3) and the same margins [94]. This alternative A-POLO strategy was adapted to the dose-escalated approach, as it allowed to treat with a comfortably full bladder.

Concerns with plan of day approach. Two main issues exist with the PoD global approach. First, the number of plans to be created is a matter of debate. With the A-POLO approach, McDonald et al. estimated that 49%, 45% and 6% of the 139 fractions were delivered using the small, intermediate and large PTV respectively. Only 12% of patients were treated with the three plans, and as high as 12% use the same plan (small) during the course of the treatment. Overall, no more than 3 plans should be generated with the PoD strategy [141].

The second issue is related to the on-line plan selection. In McDonald et al.'s study, clinicians and radiographers underwent training in plan selection before enrollment. Concordance between the plans selected online and offline by a single expert was as high as 91% [141]. The implementation of a training program is associated with continual assessment to improve the radiographer-led plan selection [147,148].

Online daily re-planning strategy. Online daily adaptive re-planning strategies require a rapid workflow that integrates online imaging, deformable image registration, contour propagation or manual delineation, plan reoptimisation, quality assurance and treatment delivery while the patient is on the couch [129,133]. Advanced technologies including MR-guided radiotherapy seem promising in order to provide a robust and fluid workflow in this perspective, with potential feasibility of real-time adaptive re-planning accounting for intra-fraction motions [149,150].

Overall benefits of adaptive radiotherapy. Overall, ART strategies have shown dosimetric benefits, mostly in terms of reduction of irradiated healthy tissue volume (27–40%) due to the reduction of CTV-PTV margins [151]. Several studies have also shown an improvement in target volume coverage [123,132,141]. No prospective trial has compared ART vs conventional radiotherapy in terms of clinical benefit, but the prospective ART trials reported overall excellent local control rate, with few late gastro-intestinal toxicity [89,103,123,132,142,143]. The PoD strategy seems to provide the optimal balance between target coverage and tissue sparing as compared to offline composite strategy [125].

The ongoing HYBRID-CRUK/12/055 trial is the first phase II randomized controlled trial to compare clinical outcome of ART versus conventional radiotherapy for bladder cancer [152]. Regarding the choice of the better ART strategy, several studies have compared different approaches [125,127,129,133,137].

Concurrent systemic treatment

In the context of bladder sparing trimodal therapy, two phase III randomized controlled trials have validated the use of concurrent systemic treatment in association with radical bladder radiotherapy.

With a median follow-up of 69.9 months, James et al. have shown that 5-FU (500 mg per square meter of body surface area per day) during fractions 1–5 and 16–20 of irradiation and mitomycin C (12 mg per square meter) on day 1 in association with bladder irradiation as compared to radiotherapy only could improve 2-year loco-regional disease free survival rates (67% vs 54%, HR = 0.68, p = 0.03) and decrease 2-year invasive loco-regional relapse rates (18% versus 32% (hazard ratio 0.57; 95% CI, 0.37–0.90; P = 0.01)), but with no benefit on OS [76]. The 10-year follow-up data presented at ASCO GU in 2017 demonstrated that locoregional control and invasive-loco-regional control were still improved with chemoradiotherapy compared to radiotherapy alone, and when known prognostic factors were considered, there was an improvement in bladder cancer specific survival, but with no difference on OS; salvage cystectomy rate was lower for concurrent chemoradiotherapy (2-year rate, 11% vs 17%, p = 0.03) [153].

Hoskin et al. have shown that hypoxic cell sensitization with carbogen and nicotinamide (CON) in association with RT compared to RT only could improve 3-year OS (59% vs 46%, p = 0.04) and 3-year relapse-free survival (54% vs 43%, p = 0.06), with no evidence of differences in late urinary or gastro-intestinal morbidity [79].

From bladder sparing trimodal therapy phase II trials, the main concurrent chemotherapy regimens may also include: cisplatin alone [22,24,77,78,81–83,85,87–89,93]; cisplatin combined with either 5-FU [10,23,26,28,94,95] or paclitaxel [25,26,88]; and low dose gemcitabine [28,84,97,98]. Outcomes for these regimens may be similar with complete response rate of approximately 70%, with local habits depending on the country. In the randomized phase II RTOG 0712 trial, Coen et al. evaluated two regimens: a cisplatin – 5FU regimen concurrently with a twice-daily RT and a gemcitabine regimen concurrently with a once-daily radiotherapy [28]. The trial was not powered to compare these regimens but to assess whether either regimen exceeded a rate of freedom from distant metastasis at 3 years (DMF3) of 75%. The DMF3 for the cisplatin – 5FU regimen and for the gemcitabine regimen were 78% and 84%, respectively, with less toxicity in the gemcitabine regimen. Based on their phase 1 trial [154], the ongoing phase 2 GETUG V04 trial compares cisplatin and gemcitabine-based strategies.

Synthesis of the guidelines

The guidelines from the working group are compiled in a summary table (Table 4). A consensus was obtained for all 34 except 4 items. The group did not obtain an agreement on the recommendation grade for the following topics: CT enhancement added value for planning, PTV margins definition for empty bladder and full bladder protocols, and PLN irradiation. High quality evidence was shown in 6 items; 8 items were considered as low quality of evidence.

Conclusions

Radical radiotherapy for localized MIBC within trimodal therapy is an established option for selected patients. However, several challenges arise when considering such treatments, mainly linked to the wide variability in position and shape of the bladder, and to the heterogeneity of chemoradiotherapy regimens reported to date. The current recommendations are proposed to homogenize the modalities of treatment both for routine clinical practice and for future clinical trials designed following the best evidence to date. Furthermore, the aim was to formulate practical recommendations for the implementation of novel techniques such as adaptive radiotherapy within radiotherapy departments.

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