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Review of hypo-fractionated radiotherapy for localized muscle invasive bladder cancer

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ABSTRACT

- The most common treatment for non-metastatic muscle invasive bladder cancer (MIBC) is radical cystectomy with pelvic lymph node dissection. For selected patients, trimodal therapy (TMT) consisting in a maximal transurethral resection of the bladder, followed by a concurrent chemotherapy and radiotherapy, spread over 5 to 7 weeks, is considered as an acceptable option. We aimed to perform a systematic review to report the current results of curative hypo-fractionated radiotherapy in terms of oncological outcomes and toxicity. In total, 5 phase III and 13 phase II trials were retained. Our review shows that TMT using hypo-fractionated radiotherapy allows a 2-year recurrence free survival rate between 43% and 83%, a 5-year OS rate going from 36% to 58%. Less than 12% of late grade ≥3 gastro-intestinal toxicities and between 4 to 46% grade ≥3 genito-urinary late toxicities were observed. This approach must be evaluated with prospective trials including quality of life scales.

1. Introduction

Every year, 2.7 million patients are diagnosed or treated for a bladder cancer in the world (Siegel et al., 2018). The incidence of bladder cancer increases with age and smoking (Antoni et al., 2017). Mortality rates vary across countries due to differences in risk factors, diagnostic practices and availability of treatments, but also because of variations in study methodology and quality of data collection (Burger et al., 2013).

The gold standard treatment for non-metastatic muscle invasive bladder cancer is radical cystectomy with pelvic lymph node dissection. However, this approach comes with a certain degree of surgical morbidity (ranges from 30% to 60%), comprises mostly post-operative complications (Huddart et al., 2017a), and peri-operative mortality rate of about 1 to 7%.

Trimodal therapy (TMT) consists of a maximal transurethral resection of the bladder, followed by a concurrent radiotherapy and chemotherapy. This bladder-sparing strategy have been considered as an acceptable alternative to radical cystectomy and, despite the promising findings of a bladder cancer definitive chemo-radiotherapy phase 3 study in terms of survival outcomes (Poortmans et al., 2008), no prospective trial has been completed comparing radical cystectomy vs.

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organ-conserving strategies; the onco-urological community lacks of level I evidence to answer that important question. In this direction, SPARE was a multicentre randomised controlled trial comparing radical cysctectomy and selective bladder preservation in patients with muscle invasive bladder cancer staged T2-3 N0 M0, fit for both treatment strategies and receiving three cycles of neoadjuvant chemotherapy. The failure of the SPARE study to accrue patients, due to the inherent difficulties to make this kind of randomization acceptable to the patients, illustrated the challenges of achieving such a comparison (Huddart et al., 2017a).

For selected patients, TMT involves external beam radiotherapy, either bi-fractionated (two times daily) (Poortmans et al., 2008; Horwich et al., 2005) or normo-fractionated (James et al., 2012; Krause et al., 2011), spread over 5 to 7 weeks. Analyzing the radiobiological rationale in the context of bladder irradiation, Maciejewski et al. (Maciejewski and Majewski, 1991) suggested that an average tumour clonogen repopulation in transitional cell cancer of the bladder accelerates after a lag period of about 5–6 weeks after the start of treatment; in this direction, a dose increment of 0.36 Gy per day is required to compensate for this repopulation. It suggests that overall treatment time is an important factor in the dose fractionation and protraction of time may have a significant impact on treatment outcome. This radiobiological rationale constitutes the basis for stimulating a wider interest in an accelerated hypo-fractionated radiotherapy approach using larger dose per fraction than the conventional 1.8–2 Gy. On the other hand, estimates of α/β for bladder tumours generally indicated low fractionation sensitivity (mostly, $\alpha/\beta = 10$ Gy), but only limited data are available, highlighting discrepancies in radiobiological analyses of bladder cancer irradiation (van Leeuwen et al., 2018). In addition, shorter overall treatment duration would be more convenient for the patient quality of life, which could be even more important for the typical bladder cancer population which can be frail and/or elderly. Moreover, from a cost-effectiveness perspective, a shorter regimen has the potential to decrease the cost per episode of care, relative to conventional treatments. Could these arguments, together with the observed advances for prostate, breast or head and neck cancers (Ko et al., 2011) in the past years, be applied to the radiotherapy of localized bladder cancer?

For bladder cancers, the hypo-fractionated radiotherapy schema has been proposed in historical clinical trials of radio-chemotherapy (Cowan et al., 2004), and more recently the interest towards this approach is growing (Huddart et al., 2013; Hafeez et al., 2017). We aimed to perform a systematic review of the literature in order to report the current results of curative hypo-fractionated radiotherapy in non-metastatic bladder cancer in terms of oncological outcomes such as local control, overall survival (OS), Pogression-Free Survival (PFS) on one hand and on the other hand in terms of patients' tolerance.

2. Materials and methods

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We searched the Medline database for articles related to bladder neoplasm and radiotherapy published between 1990 and December 2017. Articles identified by searching references from candidate articles were also included in our analysis.

The following terms were used in the extensive search: bladder neoplasm and radiotherapy. Medical Subject Heading (MeSH) phrases included: ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields]) AND ((Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp]) AND "humans"[MeSH Terms]).

We included published full articles concerning humans and written in English. We included articles concerning phase III or phase II studies, in a population of patients mostly presenting muscle-invasive bladder cancers (≥T2 disease), with predominant urothelial carcinoma histology, without metastases, treated by hypo-fractionated radiotherapy with a curative intent. We considered studies involving moderate hypofractionation (doses of 2.5–4 Gy per fraction) and extreme hypofractionation (5–7 Gy in 4–7 fractions), excluding stereotactic body radiation therapy. In order to ensure robust results, we excluded conference abstracts/communications, letter to editors, case reports, reviews (accepted if they integrate a meta-analysis), guidelines and article comments. In case of overlapping studies from the same team or similar centers, with the same objective, the more recent publication was selected. Articles were excluded if they could not be accessed/retrieved, were published in a language other than English, focused on a non-urothelial histology, included mainly patients presenting with a noninvasive bladder cancer or a tumor of the higher urinary tract, reported on trials without a well-defined toxicity or oncological objective, or used approaches involving heavy ions, neo-adjuvant, adjuvant or palliative radiation treatments.

We retrieved 159 publications from PubMed. Two authors (PS and FA) independently reviewed the titles and abstracts of the 159 articles and excluded 93 based on the above-mentioned exclusion criteria. In case of uncertainty in the abstract or title, the full text was read and discussed by all co-authors to decide whether to include the article or not.

A second comprehensive analysis was carried out by reading the full text of all papers assessed for eligibility; a final consensus on 18 studies was obtained. The PRISMA flow-chart is presented in Fig. 1.

3. Results

3.1. Clinical and pathological characteristics of the population in studies using hypo-fractionation for the treatment of localized bladder cancer

In total, five phase III trials (Tables 1 and 2) and 13 phase II trials (Tables 3 and 4), including 2016 treated patients with transitional cell carcinoma were retained. Median age of patients cohorts ranged from 65 years to 86 years with a favorable (0–1) ECOG PS in the phase 3 trials. Tumoral stage ranged from T1 grade3 to T4a, with no lymph node involvement on initial imaging.

Neo-adjuvant platinum-based chemotherapy was used for all patients in the SPARE trial (Huddart et al., 2017a), for 22% and 24% in the two arms of Huddart et al. study (Huddart et al., 2013) and in 32.8% of the patients in the study from (James et al. (2012)). In the study reported by Thompson et al., patients were treated with gemcitabine alone (Thompson et al., 2017).

3.2. Results for hypo-fractionated irradiation alone or in combination with systemic agents for localized bladder cancer

3.2.1. Exclusive radiotherapy or in combination with radio-protective agents or radiosensitizers

3.2.1.1. Exclusive radiotherapy. In three phase II (Hafeez et al., 2017; Scholten et al., 1997; Jose et al., 1999) and one phase III trials (Cowan et al., 2004), patients were treated with radiotherapy alone without systemic therapy. The total dose varied from 30 to 57.5 Gy, with daily (ranging from 2.63 to 3.44 Gy), weekly (6 Gy/week) or bi-weekly (12 Gy/week) fractions.

Significant acute genito-urinary (GU) and gastro-intestinal (GI) toxicities (WHO Toxicity > 2 or CTCAE v.3.0 > 2 or equivalent according to other scales) ranged from 10% to 58% and from 4% to 62%, respectively. In terms of moderate-to-severe long-term toxicities (RTOG > 2, WHO Toxicity > 2), authors observed toxicity rates between 11% and 13%. There was no homogeneity in the scales used to evaluate tolerance. Local control rates at 2 years varied between 45% and 83% excepted in the study from (Jose et al. (1999)), whose local control was around 20%; in this study, patients were more advanced in

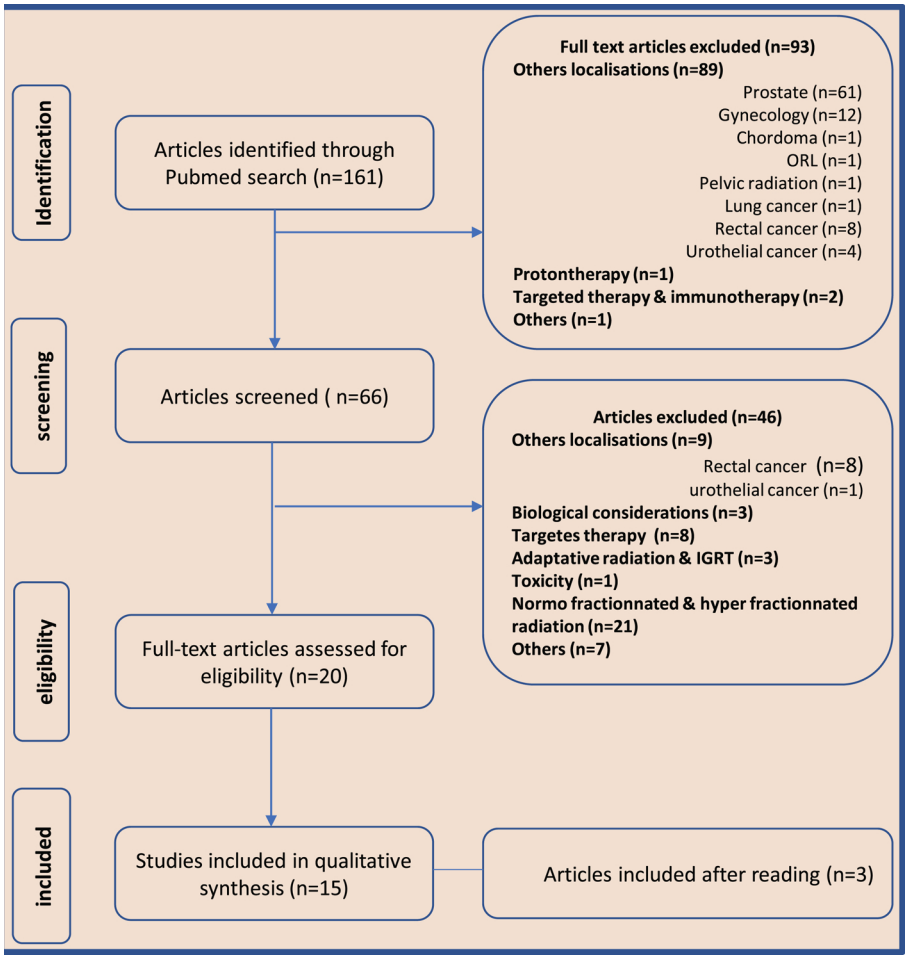

Fig. 1. The PRISMA flow chart depicting the process for the systematic literature search and selection of studies.

median age (81 years [71–95]) and considered clinically unfit to receive a normo-fractionated treatment. In these studies of radiotherapy alone, OS rates varied between 45% and 58%.

3.2.1.2. Radiotherapy in combination with radio-protective agents or radiosensitizers. – ARCON and radiotherapy

Hyperbaric oxygen and misonidazole act as radiosensitizers able to reduce intra-tumoral hypoxic phenomena.

Nicotinamide reduces hypo-vascularization allowing to maintain local perfusion (Overgaard, 1994). Based on this rationale, this approach was studied in aero-digestive cancers (Kaanders et al., 2002). In parallel, Hoskin et al. recommended the use of ARCON (nicotinamide and carbogen) in combination with radiotherapy in phase II (Hoskin et al., 2009a; Hoskin et al., 1997; Hoskin et al., 1999), and then phase III (Hoskin et al., 2010; Hoskin et al., 2009b) trials. Radiotherapy was delivered daily using a moderate hypo-fractionation schedule of 50–52.5 Gy in 20 fractions over 4 weeks (Hoskin et al., 2009b). At 3 years, severe GU and GI toxicities ranged, respectively, from 32% to 39% and from 5% to 7% according to the SOMA/LENT scale. These studies showed a satisfactory local control confirmed by cystoscopy at 6 months with a trend in favor of the ARCON arm. PFS at 3 years was 54% versus 43% ($p = 0.06$) and 5-year OS rate 50% versus 39% ($p = 0.04$) in favor of radiotherapy associated to ARCON.

– Amifostine and radiotherapy

(Panteliadou et al. (2012)) used amifostine combined to radiotherapy with the aim of optimizing the tolerance of organs at risk (digestive and genito-urinary structures). Amifostine, ethanethiol 2-[(3-aminopropyl) amino]-dihydrogen phosphate (ester), is an organic thiophosphate that, in animal models, selectively protects healthy tissues but not tumors from ionizing radiations, chemotherapy agents (classical alkylating agents such as cyclophosphamide and non-classical agents such as mitomycin C) and platinum analogues that target deoxyribonucleic acid (DNA). In a cohort of 82 patients treated for bladder cancer with radiotherapy, the dose of amifostine was increased and adapted to digestive toxicity. Fifty percent of patients received concomitant anthracycline-based chemotherapy every two weeks. Conformational radiotherapy was delivered with a technique known as "field in the field" to achieve a total dose of 51 Gy (15 x 3.4 Gy) on the bladder and 37.8 Gy on the pelvis (14 x 2.7 Gy), over 19 days. Long-term GU toxicity incidence rate was less than 2.5% with mainly incontinence, dysuria (increased urinary frequency), and a hematuria. With a median follow-up of 21 months [range, 2–63 months], complete response, 3-year local control and specific survival were 86.6%, 56% and 63%, respectively (Hussain et al., 2004).

3.2.2. Radio-chemotherapy

3.2.2.1. Mitomycin with concomitant radiotherapy. In a phase II study (n = 41 patients), Hussain et al. (2004) evaluated TMT using Mitomycin based regimen. PFS rate at 2-years was about 76% with an OS rate at 5 years of 36% [20–52].

James et al's phase III study (Huddart et al., 2017a) in which patients were randomized to receive either exclusive radiotherapy or combined radiotherapy with mitomycin C and fluorouracil, showed an improvement in the 2-year PFS rate in favor of the combination arm (67% [range, 59–74] vs 54% [range, 46–62]; $p = 0.03$). This advantage was not reflected in OS, which increased from 35% [28–43] to 48% [40–55] but did not reach significance ($p = 0.16$). Concomitant chemotherapy scheme was mitomycin C, administered on the first day of

Table 1
Summary of phase III trials evaluating a hypo-fractionated radiotherapy approach: description of patients and treatment.

Phase	Year	Authors	Name of study	n.	Median age	PS	Prior treatment (NAC/ TURB)	Stade T	Stade N	Histology	Total dose
3	2017	Huddart & al.	SPARE	45	65,7 [37,9–81,1]	0-1	100% gemcis	T2-T3	N0	TCC	55 Gy 64Gy
3	2013	Huddart & al.	BC2001/WBRT Vs PBRT +/- CT	219	74 [66,6-79]	0-1-2	23% cisplatyl (22 and 24% on each arm)	T2- T4a	N0	TCC	55 Gy 64 Gy
3	2012	James & al.	RCT Vs RT	360	71,9 [64,1–76,2]	0-1-2	32,80% 2,5% without TURB	T2-T4a	N0	97,8% TCC ADK/TCC/ SCC	55 Gy 64 Gy
3	2009	Hoskin & al.	RT Vs RTCON	322	74[51-90]	NR	complete resection 41% et 38%	T1-T4b	N0	TCC	55 Gy 64 Gy
3	2004	Cowan & al.	WBRT Vs PBRT(4 w or 3 w)	149	67,4 [40-82] 672[41-80] 678[46-76]	O-1 (88%) (89%) (84%)	TURB	T1 -T4	NO	ADK/TCC/ SCC	52,5Gy 575 Gy 55 Gy

Phase	Fraction	Duration	Modality of RT	Concurrent tretament	Toxicity: scale	Acute GU Toxicity	Acute GI toxicity	Late GU Toxicity	Late GI toxicity	Sexual dysfunction	PFS at 2 y.	OS at 5 y.
3	20 32	4 w. 6,5 w.	3D	∅	CTCAE v.3	RC:70% Vs SBP 36%(GU& GI) Tiredness & nycturia		NR	NR	NR	RC: 153%[5,2-40,5%] Vs SBP: 689%[42,5–91,5]	NR
3	20 32	4 w. 6,5 w.	3D	Randomised CT	RTOG/CTC	15,90%	360%	Cumulative toxicity : 13% (RTOG) Vs 46% (20% without sexual dysfunction)			61% [50-71] and 64%[52-73]	38% [28-47] & 44%[34-53]
3	20 32	4 w. 6,5 w.	NR	CT 5FU MMC RT only	CTCAE /RTOG/ LENT SOMA	21,3 & 21,4 CTCAE	9,6 et 2,7%	RTOG: 4,6-5,2%. LENT/SOM 34,4-35,8%		NR	67%[59-74] 54%[46-62]	48%[40-55] 35%[28-43]
3	20	4 w.	3D	ARCON	CTC v.2	4-15%	25% NV & one toxic death	32-39% 5-7% at 3 y. at 3 y.		NR	at 3 y.: 54%	50%
	32	6,5 w.		RT only	SOMA/LENT	7-18%					43%	39%
3	20 20 16	4 w. 4 w. 3 w.	IGRT 3D	NA	WHO toxicity	50% [45-55%]	62% [50-65]	4-18% 8-12%			at 2 y.: 68% WB, 63% PB4, 51%PB3 at 3 y.: 58% WB, 59%PB4, 34% PB3	58%

Legend: PS: performans statut; NAC: neo adjuvant chemotherapy; TURB: transurethral resection of the bladder; GU: genito urinary; GI: gastro intestinal,NV: nausea & vomiting; RC: Radical cystectomy; SBP: selective bladder preservation; MMC: mytomicin C; 5FU: 5 fluoro uracile; ARCON: Accelerated radiotherapy carbogen and nicotinamide; Gemcis: gemcitabine + cisplatin; TCC: transitional cell carcinoma; ADK: adenocarcinoma ; SCC: squamous cell carcinoma; RC: radical cystectomy; SBP: sparing bladder preservation; WBRT: whole bladder radiotherapy; PBRT: partial bladder radiotherapy; IGRT: Image-guided radiation therapy NR: not mentionned; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiation; NA: not applicable;RTCON: radiotherapy and carbogen & nicotinamide; w.:week; y.:year.

Table 2
Summary of phase III trials evaluating a hypo-fractionated radiotherapy approach: toxicities and results.

Phase	Year	Authors	Name of study	n.	Median age	PS	Prior treatment (NAC/ TURB)	Stade T	Stade N	Histology	Total dose
3	2017	Huddart & al.	SPARE	45	65,7 [37,9–81,1]	0-1	100% gemcis	T2-T3	N0	TCC	55 Gy 64Gy
3	2013	Huddart & al.	BC2001/WBRT Vs PBRT +/- CT	219	74 [66,6-79]	0-1-2	23% cisplatyl (22 and 24% on each arm)	T2- T4a	N0	TCC	55 Gy 64 Gy
3	2012	James & al.	RCT Vs RT	360	71,9 [64,1–76,2]	0-1-2	32,80% 2,5% without TURB	T2-T4a	N0	97,8% TCC ADK/TCC/ SCC	55 Gy 64 Gy
3	2009	Hoskin & al.	RT Vs RTCON	322	74[51-90]	NR	complete resection 41% et 38%	T1-T4b	N0	TCC	55 Gy 64 Gy
3	2004	Cowan & al.	WBRT Vs PBRT(4 w or 3 w)	149	67,4 [40-82] 672[41-80] 678[46-76]	O-1 (88%) (89%) (84%)	TURB	T1 -T4	NO	ADK/TCC/ SCC	52,5Gy 575 Gy 55 Gy

Phase	Fraction	Duration	Modality of RT	Concurrent tretament	Toxicity: scale	Acute GU Toxicity	Acute GI toxicity	Late GU Toxicity	Late GI toxicity	Sexual dysfunction	PFS at 2 y.	OS at 5 y.
3	20 32	4 w. 6,5 w.	3D	∅	CTCAE v.3	RC:70% Vs SBP 36%(GU& GI) Tiredness & nycturia		NR	NR	NR	RC: 153%[5,2-40,5%] Vs SBP: 689%[42,5–91,5]	NR
3	20 32	4 w. 6,5 w.	3D	Randomised CT	RTOG/CTC	15,90%	360%	Cumulative toxicity : 13% (RTOG) Vs 46% (20% without sexual dysfunction)			61% [50-71] and 64%[52-73]	38% [28-47] & 44%[34-53]
3	20 32	4 w. 6,5 w.	NR	CT 5FU MMC RT only	CTCAE /RTOG/ LENT SOMA	21,3 & 21,4 CTCAE	9,6 et 2,7%	RTOG: 4,6-5,2%. LENT/SOM 34,4-35,8%		NR	67%[59-74] 54%[46-62]	48%[40-55] 35%[28-43]
3	20	4 w.	3D	ARCON	CTC v.2	4-15%	25% NV & one toxic death	32-39% 5-7% at 3 y. at 3 y.		NR	at 3 y.: 54%	50%
	32	6,5 w.		RT only	SOMA/LENT	7-18%					43%	39%
3	20 20 16	4 w. 4 w. 3 w.	IGRT 3D	NA	WHO toxicity	50% [45-55%]	62% [50-65]	4-18% 8-12%			at 2 y.: 68% WB, 63% PB4, 51%PB3 at 3 y.: 58% WB, 59%PB4, 34% PB3	58%

Legend: PS: performans statut; NAC: neo adjuvant chemotherapy; TURB: transurethral resection of the bladder; MMC: mytomicin C; 5FU: 5 fluoro uracile; ARCON: Accelerated radiotherapy carbogen and nicotinamide; Gemcis: gemcitabine + cisplatin; TCC: transitional cell carcinoma; ADK: adenocarcinoma ; SCC: squamous cell carcinoma; WBRT: whole bladder radiotherapy; PBRT: partial bladder radiotherapy; IGRT: Image-guided radiation therapy NR: not mentionned; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiation; NA: not applicable; RTCON: radiotherapy and carbogen & nicotinamide; w.:week; y.:year.

Table 3
Summary of phase II trials evaluating a hypo-fractionated radiotherapy approach: description of treatment and patients.

Phase	Year	Authors	Name of study	n.	Median age	PS	Prior treatment (NAC/ TURB)	Stade T	Stade N	Histology	Total dose (Gy)	Fraction (n.)	Duration	Modality of RT	Concurrent tretament
2	2017	Thompson & al.	GemX prior NAC	78	67.5[53-78] 75.5[54-82]	0-2	resection +/- NAC	T2-T4	NR	TCC & others	52.5	20	28 d.	3D	Gem J1,J8,J15,J22
2	2017	Hafeez & al	Adaptatif hypofrac	55	86 [68-97]	WHO 0-3 Charlson 0-5	NR	T2-T4a	N1-N3 (3) M1 (2)	TCC &others	36 (Hoskin et al., 2010; Hoskin et al., 2009b; Panteliadou et al., 2012; Hussain et al., 2004; Orsatti et al., 1995; Choudhury et al., 2011; Efstathiou et al., 2012; Giacalone et al., 2017; Kachnic et al., 1997; Kijima et al., 2019; Huddart et al., 2017b; Kouloulias et al., 2013; Tunio et al., 2012)	6(Huddart et al., 2017a; Poortmans et al., 2008; Horwich et al., 2005)w.	6 (Huddart et al., 2017a; Poortmans et al., 2008; Horwich et al., 2005)w.	IGRT/plan of the day	NA
2	2011	Choudhury & al	CRT gemcitabine	50	67 [49-84]	WHO 0-2	resection	T2-T3	N0M0	TCC & others	52.5	20	4 w.	3D	Gem J1,8,15,22
2	2010	Panteliadou & al.	HypoARC	82	75 [55-88]	WHO O-1	resection or intra vesical CT	T1-T4	N0&N1	TCC	51 & 37.8	15	19 d.	SIB 3D	Amifostine Doxorubicine (50%)
2	2009	Hoskin & al. (OS & PFS)	Accelerated RT ARCON	105	74 [48-85]	NR	NR	T1G2-T4G2	NR	TCC & others	50-55	20	4 w.	3D	ARCON
2	2005	Hoskin & al. Phase II Tox	Accelerated RT ARCON	105	74 [38-87]	NR	NR	T1G2-T4G2	NR	TCC & others	50-55	20	4 w.	3D	ARCON
2	2004	Hussain & al.	CRT 5FU-MMC	41	68 [58-77]	0-2	No	T2-T4	N0/Nx M0	TCC	55	20	4 w.	3D	5FU MMC
2	2003	Pos & al.	SIB	50	79 [72-86]	WHO 0-3	resection	T2-T4	NR	TCC	40/55 Gy	20	4 w. / 27 d. (Hoskin et al., 1999; Hoskin et al., 2010; Hoskin et al., 2009b; Panteliadou et al., 2012; Hussain et al., 2004; Orsatti et al., 1995; Choudhury et al., 2011; Efstathiou et al., 2012)	SIB 3D	
2	1999	Jose & al.	RT hypofrac	65	81 [71-95]	unfit	resection	T2-T4	N0-N3 M1	TCC &SCC	30-36Gy	5-6	5-6 w.	3D	
2	1999	Hoskin & al.	carb +/-nic	61	68[48-83] 67[46-81]	NR	resection	T1-T3	NR	TCC	50-55 Gy	20	4 w.	3D	carbogene Nicotinamide
2	1997	Hoskin & al.	ARCON A/ Carb B/Nic C/ both	30	66/69/69	NR	NR	T1 G3-T3b	NR	NR	50 52.5Gy	20	4 w.	3D	NIC/ CARB/ both
2	1996	Scholten & al.	Hypofr 2D	123	65[37-86]	NR	NR	T2-T3	N0	TCC	36	2*6Gy /w.	18 d.	2D	no
2	1995	Orsatti & al.	Alternating CRT	76	67[44-77]	ECOG 0-1	Resection	T1-T4	N0	NR	40 50	2*10 2*10	5 w. 5 w.	3D	5FU Cispl 5FU MTX

Legend: PS: performans statut; GemX: gemcitabine + radiation; NAC: neo adjuvant chemotherapy; TURB: transurethral resection of the bladder; MMC: mytomicin C; MTX: methotrexate; 5FU: 5 fluoro uracile; ARCON: Accelerated radiotherapy carbogen and nicotinamide; Gemcis: gemcitabine + cisplatin; TCC: transitional cell carcinoma; ADK: adenocarcinoma ; SCC: squamous cell carcinoma; WBRT: whole bladder radiotherapy; PBRT: partial bladder radiotherapy; IGRT: Image-guided radiation therapy NR: not mentionned; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiation; NA: not applicable; RTCON: radiotherapy and carbogen & nicotinamide;CARB: carbogene; NIC: nicotinamide; w.:week; y.:year.

Table 4
Summary of phase II trials evaluating a hypo-fractionated radiotherapy approach: toxicities and results.

Phase	Year	Authors	Name of study	Toxicity scale	Acute GU Toxicity	Acute GI toxicity	Late GU Toxicity	Late GI toxicity	Sexual toxicity	PFS at 2 years	OS at 5 years
2	2017	Thompson & al.	GemX NAC + GemX	RTOG LENT SOMA	7% 8%	18% 20%	0% 0%	5% 0%	NR	65% [48-87] 81%[68-96]	NR
2	2017	Hafeez & al	Adaptatif hypofrac	CTCAE v3.0 Acute tox.RTOG late tox.	58%	42%	4%	4%	NR	83% [92- 71]	63% (1y.)
2	2011	Choudhury & al	CRT gemcitabine	RTOG acute radiation scoring criteria LENT-SOMA RTOG/EORTC late radiation morbidity SS	NR	NR	. + 0,5 (ns)	0 (ns)	. + 1,5 (ns)	80%	61%
2	2010	Panteliadou M. & al	HypoARC	CTC v.2 LENT- SOMA	11% frequency 1% dysuria	1% proctitis 8% diarrhea	1% dysuria, hematuria, incontinence	0%	NR	63%	Specific survival 63% at 3 y.
2	2009	Hoskin & al. (OS & PFS)	Accelerated RT ARCON	NR	NR	NR	10-25% at 5 y.	3-5 % at 5y.	NR	44%	38%
2	2005	Hoskin & al. Phase II Tox	Accelerated RT ARCON	recording mobidity 1989	41% 56%	96% 76%	25% hematuria & 16% dysuria	6%	NR	At 3y. :53%43%	*
2	2004	Hussain & al.	RCT 5FU-MMC	NCI grading system	2%	10%	NR	NR	NR	76%	36%
2	2003	Pos & al.	SIB	EORTC/RTOG	14% 10%	4%	13% 11%	2%	NR	60%	45%
2	1999	Jose & al.	RT hypofrac	RTOG grading system	20%	4%	11%	12%	NR	21%	NR
2	1999	Hoskin & al.	carb+/-nic	scoring system of Dische & al.	nycturia 5 times	5 bowel mvt	3	1	NR	55% at 2y.	65% at 2y.
2	1997	Hoskin & al.	ARCON A/carb B/Nic C/both	Dische scoring system	Fcy/d.:6•	Fcy /d.:4•	NR	NR	NR	at 6 m.: 70-90%	NR
2	1996	Scholten & al.	Hypofrac 2D	RTOG	0%	0%	NR	NR	NR	40%	Specific survival at 5 y. 48%[39-58]
2	1995	Orsatti & al.	Alternating CRT	WHO toxicity	18%	17%	0%	0%	NR	81%	42% at 6 y.

Legend: NAC: neo adjuvant chemotherapy; GU: genito urinary; GI: gastro intestinal, MMC: mytomicin C; 5FU: 5 fluoro uracile; ARCON: Accelerated radiotherapy carbogen and nicotinamide; NR: not mentionned; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiation; RTCON: radiotherapy and carbogen & nicotinamide; w.:week; y.:year; d.: day; m.: month; mvt: movement;hypofrac: hypofractioned; Carb: carbogene; Nic: nicotinamide; GemX: gemcitabine aand radiation; SIB: simultaneous integrated boost; ns: no significant.

irradiation, combined with fluorouracil from D1 to D5 and from D16 to D20.

Radiotherapy was delivered with two different schedules: 64 Gy in 32 fractions or 55 Gy in 20 fractions, with no significant difference in terms of loco-regional disease-free survival between arms (p = 0.59). According to consensual and validated scales (NCI CTCAE, RTOG, LENT/SOMA), there was no difference in terms of long-term toxicity depending on the irradiation protocol. Grade 3 or 4 adverse events were slightly more common in the chemo-radiotherapy group than in the radiotherapy alone group during the treatment (36.0% vs. 27.5%, p = 0.07) but not during follow-up (8.3% vs. 15.7%, p = 0.07).

3.2.2.2. Gemcitabine with concomitant radiotherapy. Choudhury et al. in a phase II study (Choudhury et al., 2011), combined hypo-fractionated radiotherapy at a dose of 52.5 Gy in 20 fractions and a weekly gemcitabine-based chemotherapy regimen (100 mg/m^2/ infusion). This was one of the only trials that evaluated, in the long term, erectile function among the quality of life (QoL) criteria. When annual late toxicity scores were compared with baseline pretreatment scores, there were no significant differences from baseline measures at 2 years for sexual, bladder, or bowel function with results judged satisfactory by the authors. PFS rate at 3 years was 82% with an OS rate at 5 years of 65%.

Thompson et al. (2017) evaluated acute and long-term grade > 2 or more GI and GU toxicity prospectively and compared two treatment arms: one arm combining a gemcitabine injection according to the same modalities as in the trial by Choudhury et al with radiotherapy delivering 52.5 Gy in 20 fractions over 28 days (GemX), and the second arm using neo-adjuvant platinum doublet chemotherapy (NeoGemX). According to the RTOG scale, acute GU toxicity rates were similar in both arms (up to 8%) and acute GI toxicities ranged from 18% to 20%. In terms of long-term GI and GU toxicity, there was no significant difference between the two treatment arms according to the LENT/SOMA score (p = 0.48 and p = 0.19, respectively).

3.2.2.3. Trials using platinum salts, methotrexate and sequential radiotherapy. Orsatti et al. (1995) proposed in 1997 an original treatment schema that involved two radiotherapy sequences within a break of one week. A total dose of 40 or 50 Gy with fractions of 2 or 2.5 Gy was delivered. A platinum-based chemotherapy or methotrexate associated to fluoro-uracil was used. Moderate to severe acute GU and GI toxicity rates according to the WHO Toxicity scale were 18% and 17% respectively, and 6-year OS rate 42%.

3.3. Irradiation and hypo-fractionation techniques reported in the literature

3.3.1. Techniques

None of the trials included in our analysis proposed intensity modulated conformational radiotherapy (IMRT). The irradiation was delivered according to a three-dimensional conformal technique and a treatment on linear accelerator with multi-leaf collimator. The oldest trials (Scholten et al., 1997) used a bi-dimensional technique with large doses per fraction and spread over a short period of time (6 Gy twice per week over 18 days).

3.3.2. Dose, fractionation and radio-biological substrate

In the hypo-fractionated studies, the doses per fraction were mainly comprised between 2.25 and 2.5 Gy, with a maximum of 6 Gy per fraction delivered weekly (Jose et al., 1999) or every two weeks (Scholten et al., 1997). (Hafeez et al. (2017)) proposed a weekly session of 6 Gy. According to the CTCAE v.3.0 scale, acute GU and GI grade 3 toxicity rates were 18% (10/55) and 4% (2/55) respectively, with no grade 4 events observed. At 1 year, 4.3% (1/23) of patients presented a GU or GI toxicity of grade > 3.

The most common schema employed doses of 50 to 55 Gy in 20 fractions ranging from 2.25 Gy/fraction to 2.75 Gy/fraction over 4 weeks (James et al., 2012; Cowan et al., 2004; Huddart et al., 2013; Hoskin et al., 2009a; Hussain et al., 2004; Choudhury et al., 2011).

From a radio-biological point of view, (Panteliadou et al. (2012)) used the formula proposed by Maciejewski et al. (Maciejewski and Majewski, 1991) to calculate the total normalized total dose (NTD) in fractions of 2 Gy (NTD = D [(α/β + d)/(α/β + 2)]), where 'D' was the total physical dose, 'd' the dose per fraction and α/β the specific tissue ratio. The corrected NTD, which takes into account the total treatment time, was calculated according to the following formula: $NTD_{(T)} = D [(\alpha/\beta + d)/(\alpha/\beta + 2)] + \lambda(Tc\text{-}T0)$, where Tc is the number of days to deliver NTD following a conventional fractionation and' λ' the daily dose estimated to compensate for a rapid tumoral repopulation.

The biological dose equivalent to 2 Gy (EQD2Gy) delivered in all studies ranged from 40 to 64 Gy and from 54 to 70.81 Gy depending on α/β ratio of 10 Gy or 3 Gy for early and late-term toxicities, respectively.

3.3.3. Radiotherapy target volumes

Clinical Target Volume (CTV) was essentially limited to empty bladder to which a systematic Planning Target Volume (PTV) margin, more or less adapted to the stage and/or to the degree of differentiation was added [1.5–3 cm]. No study used IMRT (Scholten et al., 1997).

The partial irradiation for the bladder, limited to the macroscopic tumor volume, did not yield favorable results in terms of GU and GI toxicity in Huddart et al's non-inferiority trial (Huddart et al., 2013).

Cowan et al. in 2004 (Cowan et al., 2004), in a phase III trial, compared equally different irradiation volumes (only intra vesical macroscopic tumor or whole bladder) and showed the absence of differences in GU and GI toxicities. There was also no difference in OS (p = 0.81). However, they observed 7% (6/89) of local intra-bladder recurrence and/or at field margins in cases of partial irradiation, without a significant difference in the rate of complete response among the three treatment arms (p = 0.6).

In case of using the hypo-fractionated approach, the concomitant prophylactic pelvic irradiation was proposed, either with a standard fractionation of 2 Gy per fraction (Pos et al., 2003), or with a higher dose as in Panteliadou et al.'s trial in 2012 (Panteliadou et al., 2012) which proposed 2.7 Gy per fraction.

GI and GU toxicities, acute and long-term ones, of grade ≥3 according to the RTOG scale were of 14% and 13% respectively for 2 Gy per fractions (Pos et al., 2003).

3.3.4. Adaptive radiotherapy

Only the trial from Hafeez et al. in 2017 (Hafeez et al., 2017) proposed a "plan of the day" (POD) adapted to bladder filling. The irradiation was delivered according to a tridimensional mode. The selected population for the study included patients not suitable for surgery. Acute GU and GI toxicity of grade 3 was of 18% and 4%, respectively, without any grade 4 toxicity according to the CTCAE v3.0 scale. Overall long-term toxicity at 6 months and 12 months decreased to 6.5% and 4.3%, respectively.

4. Discussion

Conducting this systematic review, we found that the conservative approach using hypo-fractionated radiotherapy allows a 2-year recurrence free survival rate between 43% and 83%, a 5-year OS rate ranging from 36% to 58%.

TMT constitutes an acceptable alternative to radical surgery in terms of survival outcomes as well as tolerance for selected patients (Horwich et al., 2005; James et al., 2012; Krause et al., 2011; Maciejewski and Majewski, 1991). In these radiotherapy studies, the population was often older than in the cystectomy series and not suitable for surgery due to comorbidities. One of the remaining questions is that, in this conservative treatment studies, the benefit on survival of neo-adjuvant chemotherapy was not clearly established, contrary to

what has been demonstrated with the radical surgery treatment (Krause et al., 2011; Efstathiou et al., 2012). Nevertheless, with a median follow up of 7.21 years, the team from Boston reported, with TMT using non-hypofractionated radiotherapy, promising updated results, revealing 5- and 10-year overall survival rates of 57% and 39%, respectively (Giacalone et al., 2017). Patients who did not respond to the conservative treatment live shorter than responders (48 vs 14 months, $p = 0.036$) and die mostly due to cancer (HR 3.865; 95% CI, 1.562–9.562) (Kachnic et al., 1997). In this direction, a promising approach could be interesting to maintain bladder function in an efficient conservation way. Selective tetramodal bladder-sparing therapy, comprising maximal transurethral resection of bladder tumour, induction chemoradiotherapy and consolidative partial cystectomy with pelvic lymph node dissection has been evaluated prospectively in 154 patients. With a median follow-up of 48 months, the 5-year muscle invasive relapse free survival was 97% in the 107 patients who completed the protocol with excellent bladder function (Kijima et al., 2019).

The hypo-fractionated schedule shows less than 12% of late grade ≥ 3 GI toxicities and between 4–46% grade ≥ 3 GU late toxicities. It appears difficult to analyze correctly the relevant degree of toxicity given the diversity of used scales. The long-term evaluation of sexual function remains largely under-evaluated too, except for Choudhury et al's trial (Choudhury et al., 2011). Other than tolerance, for responder patients, the rate of functional bladder in place seems correlated with good quality of life in the long term (Kachnic et al., 1997); a trial are currently ongoing to address this matter (NCT02688348). Hypo-fractionated irradiation of localized bladder tumors could lead to optimizing patients' QoL. Pleading for this hypo-fractionated irradiation, we can point out that the long-term tolerance seems to be similar to that of normo-fractionated radiotherapy series.

Furthermore, it represents a medico-economic advantage (Huddart et al., 2017b) compared to two-alternative schemas previously discussed by radio-biologists (Kouloulias et al., 2013). In this regard, the hypo-fractionated model, spread over 4–5 weeks, remains coherent concerning tumoral repopulation. The schema the most commonly reported and supported in the literature is that of 50–55 Gy in 20 fractions over 4 weeks (James et al., 2012; Huddart et al., 2013; Hoskin et al., 2010; Hoskin et al., 2009b; Hussain et al., 2004).

Very few prospective trials have evaluated the input/contribution of IGRT : the "plan of the day" strategy in Hafeez et al's study (Hafeez et al., 2017) presented the advantage of sparing adjacent digestive structures while covering the target volumes in an optimized manner, by adapting the irradiation volume depending on the bladder repletion after routine/daily imaging control. None of the studies included in our review used IMRT; with the purpose of decreasing/limiting pelvic toxicity, especially GI, adaptive radiotherapy (NCT01142102, NCT01000129) and the use of modern irradiation techniques are currently being evaluated (NCT00350688). These modern strategies could have an additional asset in terms of tolerance, consolidating the possibility of using the "moderate" hypo-fractionation for patients with muscle invasive bladder cancer (Huddart et al., 2017b).

In terms of target volumes definition, partial bladder irradiation limited to the macroscopic tumor volume does not appear to reduce treatment toxicity, without any benefit in terms of local control (Huddart et al., 2013). In addition, in the conservative approach, there is no proof on the benefit of a pelvic lymph-node irradiation (Kouloulias et al., 2013). While there is no conclusive evidence to support one target volume over another, the current weight of the literature likely support targeting only the whole bladder in most patients with N0 disease.

The use of radio-sensitizers and/or radio-protective agents also presents a clinical interest but no comparison exists between the different agents used in the literature. Moreover, in daily practice, concomitant chemotherapy appears to be easier to handle in routine clinical practice. Both Choudhury et al. and the pooled analysis of Caffo et al. strengthens the evidence that chemoradiotherapy regimens with concurrent gemcitabine are feasible and well tolerated (Choudhury et al., 2011; Caffo et al., 2016). The recent identification of multiple distinct molecular subtypes of muscle-invasive bladder cancer (MIBC) can be integrated in a patient/tumor personnalised strategy (González Del Alba et al., 2017) and ongoing phase II trials combining hypofractionated radiotherapy and immunotherapy represent also a future perspective (NCT02621151, NCT03419130).

5. Conclusion

TMT is a valuable alternative to cystectomy in selected patients with localized muscle invasive bladder cancer, particularly suitable for elderly patients for whom bladder cancer incidence is high. The hypofractionated schema shows valuable oncologic outcomes and a heterogeneous gastro-intestinal tolerance in published studies. It addresses both a limitation of time constraints, based on a radiobiological rationale and a literature supply. This hypo-fractionated approach must be evaluated with the use of modern radiotherapy techniques such as adaptive radiotherapy in prospective trials including tolerance and quality of life evaluations.

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