



Bladder preservation therapy as radical treatment in muscle invasive bladder cancer patients and their quality of life.

Dr Mohd. Waseem Raza¹, Dr Archana Singh^{2*}, Dr Arpit Dwivedi³, Dr S N Prasad⁴

1. Assistant professor radiotherapy, JK cancer institute Gsvm medical college Kanpur.
2. Assistant professor radiotherapy, JK cancer institute Gsvm medical college Kanpur.
3. Junior resident radiotherapy, JK cancer institute Gsvm medical college Kanpur.
4. Professor radiotherapy, JK cancer institute Gsvm medical college Kanpur.

Corresponding Author: Dr Archana Singh. Assistant professor radiotherapy, JK cancer institute Gsvm medical college Kanpur.

Copy Right: © 2022 Dr Archana Singh, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received Date: May 18, 2022

Published Date: June 01, 2022

Abstract

Medically operable muscle-invasive bladder cancer(MIBC) can be curatively managed by (a) selective trimodality therapy that can preserve the bladder, (b) partial cystectomy and lymph node dissection or(c) radical cystectomy and lymph node dissection.For surgical approaches there is vital role chemotherapy. In trimodality approach trans urethral resection of bladder tumor (TURBT) is followed by chemoradiation, a continuous course may be employed, or the course can be split, with a break to assess for response and allow for early salvage cystectomy. Although radical cystectomy and bladder-preserving selective trimodality therapy have not been compared in a randomized fashion they appear to have similar rates of cure in selected populations. Recently, different molecular biomarkers have come into picture which can help in customization treatment of bladder cancer patients. A personalized treatment plan and further refinements of bladder preservation protocols are expected to improve treatment outcomes.This review aims at bladder preservation approaches with curative intent and at the same time omitting patients from radical surgical approaches thereby preventing morbidity and improving Quality of Life (QOL) of patients.

Keywords: Muscle invasive bladder cancer (MIBC); trimodality therapy; chemoradiation; biomarkers; quality of life

Introduction

573,278 bladder cancer case are nearly estimated in the population as per GLOBOCAN2020 placing bladder cancer as the 10th most commonly diagnosed cancer in the world. Nearly 440,864 new cases of bladder cancer in men worldwide (4.4% of total new cases). Bladder cancer is the 6th most commonly diagnosed cancer in men worldwide [1] MIBC, (cT2-4aN0M0) accounts for approximately 25–30% of all bladder cancer cases, requiring aggressive management as compared to nonmuscle invasive cancer [2], and radical cystectomy (RC) has been widely accepted as the standard treatment [3].

Radical cystectomy

In this surgical procedure resection of the whole bladder alongwith perivisceral fat, pelvic peritoneum and distal part of ureters is performed. In men, the prostate and seminal vesicles are also removed, wherein women, the anterior vaginal wall, uterus, fallopian tubes, and ovaries are also removed.[4] Pelvic lymph nodes dissection essentially performed with removal of the obturator, internal iliac, external iliac, and distal common iliac nodes. Infection, wound dehiscence, ileus, obstruction deep vein thrombosis, late stricture of the ureteroenteric anastomosis, erectile/sexual dysfunction, even death is recorded as important complications associated with the procedure. [5-8]. About 71% to 74% of patients found to develop deranged renal function.[9] . With the surgical advancement in techniques reduced perioperative mortality has reduced from 2.5% to < 1% alongwith other complications but no change in rate of perioperative morbidity (27%-64%).[5-8] Complications like haemorrhage, deep vein thrombosis, pulmonary embolism, and infection approximates upto 64% and usually found in comorbid patients. Therefore, key for fruitful surgery lies in selecting patients beforehand.[10] Robotic surgery yield's no benefit in acute morbidity over open surgery.[11] Trimodality therapy is advantageous not only in regards of preserving bladder but also maintain bowel in almost 70%cases and sexual functions in 50%. [12]

Neoadjuvant chemotherapy followed by cystectomy

Standard of care in MIBC when not opting for bladder preservation is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection. Table1 showing Combined therapy showed median survival of 77months vs 46 months in surgery arm in SWOG 8710 with 317 patients over 11years [13] .Also Significantly reduced residual disease in combined therapy group as compared to cystectomy group (38 percent vs. 15 percent, P<0.001). Increased overall survival from 30% to 36% in cystectomy vs combined therapy group over 10yrs follow up was recorded in Medical Research Council/European Organization for Research and Treatment of Cancer (MRC/EORTC) BA06 30894.[14] Meta-analysis performed including 11 randomized trials with approximately 3005 patients reported neoadjuvant platinum-based combination chemotherapy significantly improved OS, with an HR of 0.86 and a 5% 5-year OS difference.Also noted that single-agent platinum was associated with significantly worse outcomes than combination chemotherapy.[15]So cisplatin based combination chemotherapy is recommended.

TABLE 1 Neoadjuvant Chemotherapy Randomized Phase III Trials [13-18]

	Number of patients	Experiment Arm	Study Arm	Survival Difference benefit	Reference
Spain/ CUETO, 1995	122	Cis/Cyst	CYST	NO	[16]
NordicCystectomy Trial 1, 1996	325	ADM-Cis-RT/Cyst	RT/Cyst	No, but 15%5-yrs OS in T3 – T4a	[15]
Abol-Enein et al 1997	194	CarboMV/Cyst	CYST	Yes ,20% 5-y OS	[18]
RTOG 89-03,1998	126	MCV/Cis-RT	CYST-RT	NO	[17]
SWOG 8710 ,2003	317	MVAC/Cyst	CYST	Yes,-5% 10-y OS	[13]
EORTC/MRC BA06 30894 ,2011	976	MCV/RT or Cyst	RT or CYST	Yes,6% 10-y OS	[14]
ADM, doxorubicin(Adriamycin); carboMV, carboplatin, methotrexate, vinblastine; Cis, Cisplatin; Cystectomy; CUETO, Spanish Urological Club for Oncological Treatment ;EORTC, European Organisation for Research and treatment of cancer ; 5 fu, 5- fluorouracil; MRC , Medical Research Council, MVAC, Methitrixate, Vinblastine, Doxorubicin and Cisplatin , MVEC, Methotrexate, Vinblastine , eprubicin, cisplatin; NCI, National Cancer Institute; OS , overall survival; RT , radiotherapy; RTOG, Radiation Therapy Oncology Group ; SWOG Southwestern Oncology Group					

Cystectomy plus adjuvant chemotherapy

The EORTC 30994 trial showed no difference in OS in patients of pT3,pT4 or N+M0 urothelial cancer randomized according to immediate vs deferred chemotherapy post cystectomy.[19] In 2005 Metaanalysis showed 25% reduction of risk of death, 9% survival benefit and 11% benefit in cisplatin based chemotherapy regimen on analysing adjuvant chemotherapy vs no chemotherapy post cystectomy. (Table 2)

TABLE 2: Adjuvant Chemotherapy Randomized Trials [21-24]

	Number of patients	Stage	Experiment Arm	Study Arm	Survival difference	References
USC/Skinner et al,1991	91	pT3/T4 NX	Cyst + CAP x4	Cyst	Yes, 24% 3yrs DFS benefit for CAP	[21]
Spain/SOGUG 99/01,2010	142	pT3/T4 N+	Cyst +PGC x4	Cyst	Yes, 29% 5yrs OS benefit for PGC	[22]
Italy/Cognetti et al,2012	194	pT2G3-4 NO-2	Cyst +GC x4	Cyst	No	[23]
Egypt/Zaghloul et al,2019	153	pT3b/T4 or N+	Cyst + GC x4 +adj RT	Cyst + adj RT	No, 10% 2-y OS benefit for GC	[24]
adj RT, Adjuvant radiotherapy; CAP, cisplatin, doxorubicin, cyclophosphamide; Cis, cisplatin; CMV, cisplatin, methotrexate, vinblastine; Cyst, cystectomy; DFS, disease-free survival; GC, gemcitabine, cisplatin; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; OS, overall survival; PGC, paclitaxel, gemcitabine, cisplatin						

Cystectomy plus radiation

Prior chemotherapy era or 1985 it was neoadjuvant radiotherapy was usual approach to treat bladder cancer, but with advent of effective chemotherapy drugs as well as complications associated with radiation and surgery leads to neoadjuvant chemotherapy to cystectomy as standard of care, and radiotherapy remain used as adjuvant in high risk cases or as salvage modality. [27-28] Locoregional recurrence usually found to be associated with Positive surgical margins, high T stage, and positive lymph nodes. [29,30]. Baumann et al, in an univariate analysis Detected 5yrs LRR free survival is more in cases with Positive margins, tumor \geq pT3, any lymph node positivity, dissected lymph nodes less than 10 in number, lymphovascular limited node dissection (< ten nodes resected), presence of uretero-hydronephrosis or lymphovascular and, a mixed histology. But in the multivariate model, only the stage of the disease (\geq pT3) (HR =3.17; P<0.01) and a limited PLND (< ten nodes resected) (HR =2.37; P<0.01) were negative predictive factors. Also three subgroups of patients according to above-mentioned risk factors with 5yrs LRR 8% in \leq pT2 cases, 23% in \leq pT3 >10 dissected lymph nodes, 42% in \geq pT3 and <10 lymph nodes dissected subsequently named as low to high risk group respectively (P<0.01)(5). For stage \leq pT2 patients, there is no indication for adjuvant radiotherapy. Finally, for patients with stage \geq pT3 and positive margins, irradiation of common iliac, internal and external iliac, and obturator regions, of the cystectomy bed and of the pre-sacral region would encompass 79% and 91% of LRR sites (18)[30] Using these features, patients can be stratified with respect to locoregional failure as follows: low risk, unchanged (pT2 or lower); intermediate risk, at least pT3, at least 10 nodes removed, and

negative margins; or high risk, at least pT3 and either positive margins or fewer than 10 nodes removed[31-32].

Bladder-Preserving Selective Trimodality Therapy

Radiotherapy was the only modality used prior to 2002 for bladder preservation. Duncan et al reported 46% of local tumor regression post radiotherapy assessed by cystoscopy along with 5 years survival of 40, 26 and 12 in stage T2, T3, T4 respectively in Edinburgh among 963 patients between 1971 and 1982.[33] Preop EBRT Pelvis with cystectomy and iliac node dissection followed by iridium implantation was done in a study Mazon et al from 1971 to 1984 with 85 patients recorded DFS 5 years of 72% in T1 cases and 55% for T2 with 16% mortality.[34] The addition of interstitial brachytherapy to EBRT appeared to improve OS and bladder-intact survival in selected patients. Not surprisingly, bladder-preserving surgery alone—partial Cystectomy or TURBT monotherapy—yielded unacceptably high recurrence rates, even with the addition of chemotherapy or radiation, a common paradigm in the 1970s through early 1990s.

Selective trimodality therapy (Table 3) requires a maximal safe TURBT followed by definitive concurrent chemoradiation. While this is the definitive management approach with the highest cure rate for medically inoperable patients, selected operable patients are also candidates for bladder preservation, offering comparable OS to radical cystectomy.[35] Superficial recurrence is managed with TURBT and intravesical treatment,[36] while salvage cystectomy is reserved for invasive recurrence.[37]

Selection criteria for selective trimodality therapy in medically operable patients

1. Clinical T2-3a bladder cancer
2. Unifocal disease
3. Less than 5 cm in maximum diameter
4. No extensive carcinoma in situ
5. Visibly complete TURBT
6. No ureteral obstruction
7. No hydronephrosis
8. Good bladder function

Hydronephrosis can be present in 15–20% of patients with bladder cancer at diagnosis [38,39]. Hydronephrosis has been shown to be an independent prognostic factor for recurrence free survival even in surgical series [40]. Patients with hydronephrosis tend to have more advanced disease with higher risk of extra vesicular disease and pelvic nodal involvement. Therefore hydronephrosis is probably not a predictive factor for poor outcomes from definitive bladder radiotherapy but rather a prognostic factor for bladder cancer. The current standard of care for bladder preservation involves TURBT followed by concurrent chemoradiation. Patients are given either radical doses and post TURBT has found CR rates of 60% to 80%, with 5-year OS of 40% to 60%. Other way is split regimen where patient is assessed by cystoscopy after 40 Gy by cystoscopy and biopsy. Patients who achieve CR are continued for radical doses and those who achieve less than CR are planned for radical cystectomy. Following bladder preservation, non-muscle-invasive recurrence is managed with TURBT and intravesicular treatment, while patients with muscle-invasive recurrence undergo salvage cystectomy.

In a phase III trial RTOG 89-03, 123 patients of T2-T4a bladder cancer were randomized with or without 2 cycles of neoadjuvant chemotherapy with methotrexate, cisplatin, and vinblastine (MCV) followed by concurrent chemoradiation with 39.6Gy and inj cisplatin 100mg/m². [41]. Cytology or biopsy proven CR patients, received a boost to 64.8 Gy with 1 cycle of cisplatin, whereas cystectomy was performed for patients with less than a CR. The CR rate was 60%. At 5-year follow-up, 5-year OS was 48% versus 49%, bladder-functioning survival was 36% versus 40%, and DM rates were 33% versus 39%, all not statistically significant. Another key study was the British BC2001 multicenter Phase III trial. [42] Patients with T2-T4a bladder cancer were randomized to definitive radiotherapy alone versus with concurrent 500 mg/m² 5-FU on days 1 to 5 and 16 to 20, and 12 mg/m² MMC on day 1. Centers prospectively elected to give 55 Gy in 20 fractions or 64 Gy in 32 fractions. At 70-month follow-up, 2-year locoregional disease-free survival was 54% for radiotherapy alone versus 67% for chemoradiotherapy, with a statistically significant unadjusted hazard ratio of 0.68. Even after adjusting for neoadjuvant chemotherapy (as well as age, performance status, stage, grade, and radiation dose), the benefit of concurrent chemoradiotherapy remained significant (HR, 0.66; 95% CI, 0.46–0.95). Locoregional DFS was likewise unaffected by neoadjuvant chemotherapy. There was a trend toward 2-year bladder preservation, with salvage cystectomy rates of 11% versus 17%. OS at 5 years was 35% versus 48% and DM rates were 11% versus 9%. Neoadjuvant chemotherapy was quite toxic, particularly with regard to sepsis and neutropenia, leading to early closure of this trial. [41] Ultimately, the authors concluded that there was no advantage to neoadjuvant MCV. However, subsequent work suggests that neoadjuvant chemotherapy may confer some benefit. [43]

In a pooled analysis of 468 largely T2-T3 patients enrolled in RTOG 88-02, 89-03, 95-06, 97-06, 99-06, and 02-33 trials, 5- and 10-year muscle invasive local failure rates were 13% and 14%, non-muscle-invasive local failure 31% and 36%, and distant failure 31% and 35%. OS rates were 57% and 36%, comparable to radical cystectomy [44]. Notably, 5- and 10-year disease-specific survival rates were 71%

and 65%, illustrating the competing risk of medical comorbidities in the bladder-preservation patient population.[45]For medically inoperable patients, management options include:

- (a) chemoradiation-based trimodality therapy;
- (b) TURBT followed by radiotherapy, with or without concurrent chemotherapy
- (c) TURBT alone.

When radiation is used for medically inoperable patients, radiation should not be delivered in a split-course fashion, as cystectomy for subcomplete response is not an option for these patients. Definitive chemoradiation offers elderly patients a safer curative option.[46]

TABLE 3. Trimodality Chemoradiation- Based Selective Bladder Preservation Cooperative Group Trials and Cystectomy Series. [41,45,47-51]

	Number of patients	Treatment After TURBT	5yrs OS	5yrs bladder intact survival	Reference
RTOG 85-12 , 1993	42	Cis-EBRT	82	42	[47]
RTOG 88-02, 1996	91	MCV/Cis-EBRT	(4y)51	4y 44	[47]
RTOG 89-03, 1998	123	+MCV/Cis-EBRT	49	38	[41]
Erlangen ,2002	415	EBRT and Cis or Carbo or Cis- 5 FU	51	42	[48]
RTOG 99-06 ,2009	80	Paclitaxel-BID EBRT	56	47	[49]
BC 2001 ,2012	182	5 Fu/MMC-EBRT	48		[50]
MGH ,2012	348	+MCV/Cis-EBRT	52	46	[51]
RTOG(pooled) ,2014	468	cT2-T4a	57	36	[45]
BC 2001 ,2012	182	cT2-T4a	48		[50]

BC, Bladder Cancer; Chemo, Chemotherapy; Cis, Cisplatin; EBRT, External Beam Radiotherapy; 5 fu, 5- fluorouracil;MGH,Massachusetts General Hospital MCV, methotrexate ,cisplatin, vinblastine; MMC, Mitoycin-C; MSKCC, Memorial Sloan Kettering Cancer Center; OS , Overall Survival; RT, Radiotherapy; RTOG, Radiation Therapy Oncology Group; SWOG, Southwestern Oncology Group;TURBT, Transurethral Research of Bladder Tumor

Quality of Life

Quality of life differs among patients undergoing cystectomy [52,53] versus radiation-based bladder preservation [54,55] and the two modalities have been compared using cross-sectional questionnaires. [56,57] As outlined later, radical cystectomy is a major surgery, one that carries major consequences related to urinary, sexual, and bowel function. In contrast to patients' concerns prior to surgery, cystectomy (and its associated creation of a stoma) does not appear to impact social life and recreation, although it may impact patient-reported sexual activity and overall physical condition. [55] It would stand to reason that continent diversion would improve quality of life, but it is unclear whether this is actually the case. [58]

Long term results of bladder function and quality of life in patients who received bladder preservation after 6.3 years of follow up showed 75% of patients maintained normal bladder function and 59% maintained satisfactory sexual function [58]. In a case control study which reported quality of life, 74% of the patients in the radiotherapy group had little or no distress from urinary symptoms [54]. In another cross-sectional multi-institutional study of 173 patients which compared long-term QOL in MIBC patients treated with bladder preservation and radical cystectomy, bladder preservation was associated with better general quality of life and bowel function compared to cystectomy while urinary quality of life was equivalent between the groups [49,59]. It is rare that palliative cystectomy is required for symptoms related to bladder preservation, with reported rates of 0% to 2% [48] with or without perioperative chemotherapy.

Radiotherapy

Radiotherapy plays vital role in preserving bladder in MIBC sustaining similar DFS & OS as of Surgery. But uncertainties still exists regarding radiotherapy like whether to irradiate whole bladder or partial bladder, elective pelvic lymph node irradiation in node negative cases ,CT simulation should be done full bladder or empty bladder, which advanced technique should be beneficial. So here are some conclusions.

Whole bladder or Partial bladder?

There was no toxicity improvement found on treating partial bladder as compared to full bladder hence whole bladder should be considered target volume [60].

Elective Pelvic LN irradiation in node negative cases ?

Pelvic Lymph node Positivity ranges from 20% to 60% in MIBC underwent cystectomy [61] .which makes elective pelvic nodal irradiation mandatory however Leissner et al reported recurrence rates as low as of 4 to 14% in radiotherapy cases without prophylactic PLN irradiation [62]. Significant incidental doses received by concerned nodes found to be the rationale behind decrease recurrence rates [63]. Therefore pelvic LN irradiation is not recommended in node negative cases.

2D/ 3DCRT/IGRT/IMRT?

Usually higher technologies recommended to improve tissue toxicity profile with similar efficacy, but during bladder preservation therapy using 3DCRT technique over IMRT, IGRT can be chosen as incidental doses to pelvic lymph nodes can decrease in view of reduced margins to CTV.[64]

Simulation full or empty bladder?

Bladder motion found to be real issue to be addressed during simulation. Bladder volume of 320ml to 450ml leading to decrease of bladder motion drastically. so when treating whole bladder, CT simulation should be done in full bladder [65]. Appropriate full bladder can be achieved by drinking 500ml of water after emptying bladder, 45min prior to CT simulation[63]. Empty bladder CT simulation is required for boost phase planning.

Target Volumes?

GTV,CTV(whole Bladder),PTV (CTV+1.5cm with extravesical extension of tumor +2cm), in case of bladder neck tumors Prostatic urethra+1.5cm in & female urethra+1cm contouring should be done,OAR should be rectum ,bowel and bilateral femur head.

Dose and fractionation?

Conventional fractional and Hypofractionation found to have similar in DFS,OS as well as toxicity. So Hypofractionation should be used as standard of care[66]. Most commonly used fractionation is Conventional fractionation to total dose ranges 60 to 64Gy. Split course radiotherapy showed no advantage over above two along with risk of tumor regrowth.[67]

Conclusion

In case of MIBC, bladder preservation can be achieved in medically operable as well as inoperable cases by carefully selecting patient for various modalities of treatment to further improve to survival benefit as well as quality of life.

References:

1. GLOBOCAN2020 https://worldbladdercancer.org/news_events/globocan-2020-bladder-cancer-10th-most-commonly-diagnosed-worldwide/)
2. VanderWalde NA, Chi MT, Hurria A, et al. Treatment of muscle invasive bladder cancer in the elderly: navigating the trade-offs of risk and benefit. *World J Urol* 2016;34:3-11.
3. Muscle-invasive and Metastatic Bladder Cancer. Available online: <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic>.
4. Dhar NB, et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol*. 2008;179(3):873–878, discussion 878.
5. Frazier HA, Robertson JE, Paulson DF. Complications of radical cystectomy and urinary diversion: a retrospective review of 675 cases in 2 decades. *J Urol*. 1992;148(5):1401–1405.
6. Chang SS, et al. Analysis of early complications after radical cystectomy: results of a collaborative care pathway. *J Urol*. 2002;167(5):2012–2016.
7. Donat SM, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. *Eur Urol*. 2009;55(1):177–185.
8. Novotny V, et al. Perioperative complications of radical cystectomy in a contemporary series. *Eur Urol*. 2007;51(2):397–401, discussion 401–402.
9. Eisenberg MS, et al. Long-term renal function outcomes after radical cystectomy. *J Urol*. 2014;191(3):619–625.
10. Chappidi MR, et al. Frailty as a marker of adverse outcomes in patients with bladder cancer undergoing radical cystectomy. *Urol Oncol*. 2016;34(6):256, e1–e6.
11. Bochner BH, et al. Comparing open radical cystectomy and robotassisted laparoscopic radical cystectomy: a randomized clinical trial. *Eur Urol*. 2015;67(6):1042–1050

12. Zietman AL, et al. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. *J Urol.* 2003;170(5):1772–1776.
13. Grossman HB, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.* 2003;349(9):859–866
14. International Collaboration of Trialists. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol.* 2011;29(16):2171.
15. Malmstrom P, Rintala E, Wahlqvist R. Five-year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: nordic cystectomy trial I. *J Urol.* 1996;155:1903–1906.
16. Martinez-Pineiro JA, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol.* 1995;153(3 Pt 2):964–973.
17. Shipley WU, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol.* 1998;16(11):3576–3583.
18. Abol-Enein, El-mekresh M, El-baz M, Ghoneim MA. Neo adjuvant chemotherapy in treatment of invasive transitional bladder cancer a controlled prospective randomized study. *Br J Urol.* 1997;80(suppl 2):49.
19. Sternberg CN, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol.* 2015;16(1):76–86.
20. Advanced Bladder Cancer Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol.* 2005;48(2):189–199, discussion 199–201.
21. Skinner DG, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol.* 1991;145(3):459–464, discussion 464–467
22. Paz-Ares L, et al. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. *J Clin Oncol.* 2010;28(18_suppl):LBA4518-LBA4518

23. Cognetti F, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol.* 2012;23(3):695–700.
24. Zaghloul MS, Christodouleas JP, Hwang WT, et al. Randomized phase III trial of adjuvant sequential chemotherapy plus radiotherapy versus adjuvant radiotherapy alone for locally advanced bladder cancer after radical cystectomy: Urothelial carcinoma subgroup analysis. in *American Society for Clinical Oncology Genitourinary Cancers Symposium.* 2019. San Francisco, CA.
25. Sell A, et al. Treatment of advanced bladder cancer category T2 T3 and T4a. A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor. DAVECA protocol 8201. Danish Vesical Cancer Group. *Scand J Urol Nephrol Suppl.* 1991;138:193–201.
26. Whitmore WF Jr, et al. Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. *J Urol.* 1977;118(1 Pt 2):184–187.
27. Cole CJ, et al. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. *Int J Radiat Oncol Biol Phys.* 1995;32(2):331–340.
28. Reisinger SA, Mohiuddin M, Mulholland SG. Combined pre- and postoperative adjuvant radiation therapy for bladder cancer—a ten year experience. *Int J Radiat Oncol Biol Phys.* 1992;24(3):463–468.
29. Christodouleas JP, Hwang WT, Baumann BC. Adjuvant radiation for locally advanced bladder cancer? A question worth asking. *Int J Radiat Oncol Biol Phys.* 2016;94(5):1040–1042.
30. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, Crundwell M, Sizer B, Sreenivasan T, Hendron C, Lewis R, Waters R, Huddart RA. BC2001 Investigators. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012;366(16):1477-88.
31. Christodouleas JP, et al. Optimizing bladder cancer locoregional failure risk stratification after radical cystectomy using SWOG 8710. *Cancer.* 2014;120(8):1272–1280
32. Baumann BC, et al. Validating a local failure risk stratification for use in prospective studies of adjuvant radiation therapy for bladder cancer. *Int J Radiat Oncol Biol Phys.* 2016;95(2):703–706. 236, 258-73
33. Duncan W, Quilty PM. The results of a series of 963 patients with transitional cell carcinoma of the urinary bladder primarily treated by radical megavoltage X-ray therapy. *Radiother Oncol.* 1986;7(4):299–310.
34. Mazon JJ, et al. Conservative treatment of bladder carcinoma by partial cystectomy and interstitial iridium 192. *Int J Radiat Oncol Biol Phys.* 1988;15(6):1323–1330.

35. Mak RH, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group
36. Zietman AL, et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology*. 2001;58(3):380–385.
37. Efstathiou JA, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol*. 2012;61(4):705–711.
38. Bartsch GC, Kuefer R, Gschwend JE, de Petriconi R, Hautmann RE, Volkmer BG. Hydronephrosis as a prognostic marker in bladder cancer in a cystectomy-only series. *Eur Urol* 2007;51(3):690-7; discussion 697-8. Epub 2006 Jul 28.
39. Halebian GE, Skinner EC, Dickinson MG, Lieskovsky G, Boyd SD, Skinner DG. Hydronephrosis as a prognostic indicator in bladder cancer patients. *J Urol* 1998;160(6 Pt 1):2011-4.
40. Bartsch GC, Kuefer R, Gschwend JE, de Petriconi R, Hautmann RE, Volkmer BG. Hydronephrosis as a prognostic marker in bladder cancer in a cystectomy-only series. *Eur Urol* 2007;51(3):690-7; discussion 697-8. Epub 2006 Jul 28.
41. Shipley WU, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*. 1998;16(11):3576–3583.
42. James ND, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. 2012;366(16):1477–1488.
43. Mirza A, Choudhury A. Bladder preservation for muscle invasive bladder cancer. *Bladder Cancer*. 2016;2(2):151–163
44. Stein JP, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*. 2001;19(3):666–675.
45. Mak RH, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol*. 2014;32(34):3801–3809.
46. Gray PJ, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *Eur Urol*. 2013;63(5):823–829
47. Tester W, et al. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. *J Clin Oncol*. 1996;14(1):119–126.

48. Rodel C, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol*. 2002;20(14):3061–3071.
49. Kaufman DS, et al. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*. 2009;73(4):833–837.
50. Huddart RA, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys*. 2013;87(2):261–269.
51. Efstathiou JA, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol*. 2012;61(4):705–711.
52. Boyd SD, et al. Quality of life survey of urinary diversion patients: comparison of ileal conduits versus continent Kock ileal reservoirs. *J Urol*. 1987;138(6):1386–1389.
53. Månsson Å, Johnson G, Månsson W. Quality of life after cystectomy comparison between patients with conduit and those with continent caecal reservoir urinary diversion. *BJU Int*. 1988;62(3):240–245.
54. Kachnic LA, et al. Combined modality treatment with selective bladder conservation for invasive bladder cancer: long-term tolerance in the female patient. *Cancer J Sci Am*. 1996;2(2):79–84
55. Lagrange J-L, et al. Quality of life assessment after concurrent chemoradiation for invasive bladder cancer: results of a multicenter prospective study (GETUG 97-015). *Int J Radiat Oncol Biol Phys*. 2011;79(1):172–178.
56. Caffo O, et al. Assessment of quality of life after cystectomy or conservative therapy for patients with infiltrating bladder carcinoma. A survey by a self-administered questionnaire. *Cancer*. 1996;78(5):1089–1097.
57. Henningsohn L, et al. Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol*. 2002;62(2):215–225.
58. National Cancer Institute Surveillance, Epidemiology, and End Results Program: Cancer Stat Facts: Bladder Cancer. 2019; Available from: <https://seer.cancer.gov/statfacts/html/urinb.html>.
59. Kimberley S, Mak, et al. Quality of life in long-term survivors of muscle-invasive bladder cancer. *J Clin Oncol* 2015;33(suppl 7; abstr 319).
60. Huddart RA, Hall E, Hussain SA, Jenkins P, Rawlings C, Tremlett J, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 Trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys* 2013;87(2):261–9.

61. Regional lymph node metastasis from bladder cancer. J A Smith Jr, W F Whitmore Jr. J Urol 1981 Nov;126(5):591-3.
62. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Leissner 1, M A Ghoneim, H Abol-Enein, J W Thüroff, L Franzaring, M Fisch, H Schulze, G Managadze, E P Allhoff, M A el-Baz, H Kastendieck, P Buhtz, S Kropf, R Hohenfellner, H K Wolf. J Urol. 2004;171(1): 139-144
63. Incidental Dose to Pelvic Nodes in Bladder-Only Radiotherapy: Is It Clinically Relevant? Shirley Lewis 1, Vedang Murthy 1, Umesh Mahantshetty 1, Shyam Kishore Shrivastava 1 Technology in Cancer Research & Treatment 2017, Vol. 16(3) 382–387 Vol. 16(3) 382–387.
64. A practical approach to bladder preservation with hypofractionated radiotherapy for localised muscle-invasive bladder cancer. R. Portner a,*, A. Bajaj b, T. Elumalai a, R. Huddart c,d, V. Murthy e, H. Nightingale a, K. Patel a, P. Sargos f, Y. Song a, P. Hoskin g,h, A. Choudhury a,h. Clinical and Translational Radiation Oncology 31 (2021) 1–7.
65. Dynamic Changes in Bladder Morphology Over Time in Cervical Cancer Patients Fu Jin, PhD1, Qiang Liu, MS2, Huanli Luo, PhD1, Rui Zhu, MS3, Yanhong Mou, MS2, Yongzhong Wu, MD1, and Ying Wang, MD1 For
66. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. Ananya Choudhury 1, Nuria Porta 2, Emma Hall 2, Yee Pei Song 3, Ruth Owen 4, Ranald MacKay 5, Catharine M L West 6, Rebecca Lewis 2, Syed A Hussain 7, Nicholas D James 8, Robert Huddart 9, Peter Hoskin 10, BC2001 and BCON investigators Lancet Oncol 2021;22 (2):246–55
67. Arafat W, Darwish A, Naoum GE, Sameh W, El Hussein G, Abd-El-Gawad F, et al. Comparison between standard and reduced volume radiotherapy in bladder preservation trimodality protocol for muscle-invasive bladder cancer patients. Ecancermedalscience 2016;10