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Review Article

Bladder Cancer Treatment: Review of Literature

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Abstract

Purpose

The aim of this study is the systematic review of external radiation therapy studies in bladder cancers.

The review of the literature is based on data from meta-analyses, randomized and prospective trials and retrospective studies. There are several reports on multimodal treatment in invasive bladder cancer: intravesical chemotherapy, surgery, neoadjuvant chemotherapy, radiotherapy and concomitant radiochemotherapy with organ preservation.

Conclusions

Sufficient data now exist to demonstrate that conservative management with organ preservation is a valuable alternative to radical cystectomy, the traditional gold standard, in invasive bladder cancer.

Keywords: Invasive Bladder Cancer; Treatment; Radiation Therapy; Radical Cystectomy;Chemotherapy; Overall Survival

Abbreviations

CDDP : Cis-diamminedichloroplatinum as Cisplatin
CCRT : Concomitant Chemioradiotherapy
CR : Complete Response
CT : Chemotherapy
CTV : Clinical Target Volume
DFS : Disease Free Survival
DSS : Disease Specific Survival
FFDM : Freedom from Distant Metastases
IMRT : Intensity Modulated Radiation Therapy
LF : Local-Regional Failures
MCV : Methotrexate, Cisplatin and Vinblastine
MVAC : Methotrexate, Vinblastine, Doxorubicin and Cisplatin
OARs : Organs at Risk
OS : Overall Survival
pCR : Pathological Complete Response
RTOG : Radiation Therapy Oncology Group
RT : Radiotherapy
TURBT : Transurethral Resection of Bladder Tumors
5-FU : 5- fluorouracil

Introduction

Most bladder cancers are transitional cell carcinomas. In 2014 in USA the incidence of new cases and deaths were 74.690 and 15.580 respectively [1].Worldwide, almost 430.000 cases were diagnosed in 2012 [2]. Bladder cancer is the 13th most common cause of cancer death worldwide, with around 165.100 deaths from bladder cancer in 2012 [3].

The successful therapy of bladder cancer was obtained with great economic burden in health care system [4] with cost from $ 96.000 to 187.000 per patients.

Incidence of bladder cancer increases with age: the median age at the diagnosis is 73 years; in fact, 70% of diagnosis occurs in patients aged 65 and older, and half of diagnosis occurs in patients older than 75 [5].

There are not many clinical studies about old patients affected by bladder cancer because comorbidity and higher risk of collateral effects of standard therapy limited their eligibility in protocols. The solution of optimal treatment should be personalized and informed by a full assessment able to predict probability incidence of side effects [6].

A comprehensive literature research was conducted using PubMed in July 2014. Relevant international articles published from 1970s to 2014 were assessed. The keywords for search purpose were: invasive bladder cancer, radiation therapy, radical cystectomy, chemotherapy, overall survival.

There are several reports on multimodal treatment in invasive bladder cancer: intravesical chemotherapy, surgery, neoadjuvant chemotherapy (CT) and radiotherapy (RT) or concomitant radiochemotherapy (CCRT) with organ preservation.

Radical cystectomy

Radical cystectomy with bilateral pelvic lymph node dissection followed by urinary diversion remains the gold standard for treating muscle-invading bladder cancer. Potential morbidity and mortality are described in literature, mainly in old patients. The study conducted by Froehner et al. showed that perioperative mortality [7] was 3-4% in 80 years old patients; conversely in young patients was 1-2%. Also post operative complications are higher in older patients. For this reason, the use of lymphadenectomy and neobladder intervention is less common in older people.

New robotic techniques or laparoscopic techniques of cystectomy are more utilized with less blood loss during surgery and short stay in hospital.

Comparison of large surgery and RT series suggests very similar long-term survival rates. However must surgical series have median age of 60 and RT series 60-80.

Bladder preservation is different in the world (10% in U.S, 25% in Sweden, 50% in U.K.) [8-10].

James in U.K.[8] showed that in patients 80 years old only 3 % went to surgery, instead 55% underwent to RT.

Munro in U.K. [9] demonstrated that in Yorkshire the ratio of surgery was 1:3; after 10 years 22% were treated with RT and 24% underwent to radical cystectomy.

Definitive Radiotherapy

RT alone applied with a curative intent was used extensively from the 1950s through the 1980s. It was inevitable that numerous studies attempted a comparison of outcome of RT with radical cystectomy. Such comparisons were very difficult, because patients selected for radical cystectomy had less advanced tumors at diagnosis, they were younger and in a better general condition than patients selected for definitive irradiation.

Patients treated by radical RT should have adequate bladder capacity, no stenotic symptoms and no incontinence (Figure 1).

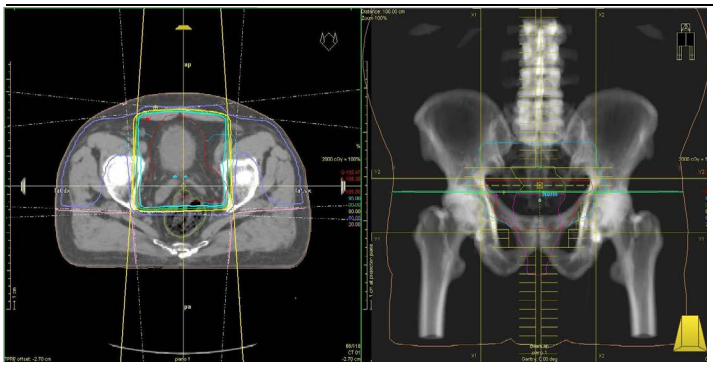

Figure 1. A digitally reconstructed radiographs, and dosimetric study of bladder irradiation.

Results reported in the literature are not significant: the 5-year survival rate for patients treated with RT alone (dose of 60–66 Gy at a 1.8- to 2-Gy daily fraction) is 32% (range 22%–50%) [11,12] (Table 1). A recent review of treatment outcomes in RT -treated patients showed that the following 5-year survival rates were different in according to the patients'staging: T1, 35%–71%; T2, 10%–59%; T3, 10%–38%; and T4, 0%–16% [14].

STUDY AND REFERENCE	N. of pts	T2	T3 (T3a/T3b)	T4	5-years overall survival
Goffinet DR et al. [15]	384	35-42	20	/	/
Yu NS et al. [16]	356	42	(35/23)	/	/
Goodman GB et al. [17]	470	/	/	/	38
Duncan W et al. [18]	963	40	26	12	30
Blandy JP et al. [19]	614	27	38	9	/
Jenkins BJ et al. [20]	182	46	35	/	40
Gospodarowicz MK et al. [21]	355	50	(38/280)	/	46
Jahnson S et al. [22]	319	31	16	6	28
Davidson SE et al. [23]	709	49	28	2	25
Greven KM et al. [24]	116	59	10	0	/
Smaaland R et al. [25]	146	26	10	/	/
Fossa SD et al. [26]	308	38	14	/	24
Vale JA et al. [27]	60	38	12	/	/
Pollack A et al. [28]	135	42	20	0	26
Moonen L et al. [29]	379	25	17	/	22
Tonoli et al. [12]	459	54	18	/	36
Langsenlehner T et al. [30]	75	34	32	9	56.9

Table 1. Survival after RT alone for muscle-invasive bladder cancer.

Preoperative radiation therapy

The largest experience (338 patients) with preoperative RT obtained pathologic downstaging in 65% of patients and complete response (CR) in 42%. The 5-year overall survival (OS) was 44% and the pelvic and distant recurrence rates were 16% and 43%, respectively [28]. A prospective randomized trial comparing preoperative RT with definitive pelvic irradiation was conducted by Bloom et al. [31]. The 5-year survival in patients receiving RT followed by cystectomy was 38% versus 29% for those treated with RT alone (not statistically significant). There was a significant survival benefit of preoperative irradiation in male patients younger than 60 years of age. Tumor-stage reduction and CR were obtained in 49% and 31% of patients, respectively, receiving preoperative RT.

Strong support for the use of preoperative irradiation in patients with T3b bladder cancer was reported by Cole et al. [32]: the 5-year local control in the preoperative group was 91% compared with 72% for those treated with radical cystectomy alone. There was also a benefit in terms of OS and disease free survival (DFS) and in freedom from distant metastases (FFDM) (not statically significant). Tumor doses were 20–50 Gy. However, a meta-analysis of five randomized trials showed no statistical difference in treatment outcomes between patients treated with preoperative RT and cystectomy alone [33]. A similar conclusion was reached in a phase III study of 140 patients comparing surgery alone with surgery and preoperative irradiation [34].

Preoperative CCRT showed better results than RT alone. In fact, in the Nordic Cystectomy Trial [35], the combination of CT (Adriamycin + Cisplatin (CDDP) for two cycles) plus RT (20 Gy in four fractions) followed by cystectomy showed a 5-year OS improvement of 15% only for T3-T4 disease compared with RT or surgery alone (p=0.03), whereas no survival benefit was found for early stages of disease (T1–T2). In the Canadian randomized study [36], concurrent CCDP improved pelvic disease control with preoperative or definitive RT compared with RT alone (p=0.038).

Postoperative radiation therapy

The main advantage of postoperative RT is the availability of pathological staging. Postoperative RT is administered to patients with extravesical disease, positive resection margins or involved pelvic lymph nodes with doses of 40–50 Gy.

Some studies reported reduction of the risk of pelvic recurrence from 30% to 50% to 10% to 20% [37-39], but some patients also received preoperative RT. Only one randomized study of radical cystectomy alone versus cystectomy and postoperative RT [40] reported a 5-year pelvic recurrence of 5% (50% in the cystectomy arm). The main disadvantage of postoperative RT is the high rate (20%–40%) of serious late gastrointestinal complications [37, 38, 41-43] for the larger volume of small bowel occupying the pelvis after cystectomy. Patients at high risk of recurrence are probably better treated with CT, which may prevent local and distant relapse and it is usually well tolerated.

An analysis of the University of Pennsylvania about cystectomy experience [44] identified three patient subgroups with significantly different local-regional failures (LF) risk: low-risk (stage ≤pT2 disease), intermediate-risk (stage ≥pT3 and ≥10 benign or malignant nodes removed at surgery), and high-risk (stage ≥pT3 and <10 benign or malignant nodes removed at surgery)—with 5-year LF rates of 8%, 23%, and 42%, respec-

tively [45].

Postoperative radiation reduced pelvic recurrences in the past, but multiple reports showed excessive gastrointestinal toxicity using pre-1980 RT techniques. Modern RT, such as image-guided intensity modulated RT and proton therapy with more precisely targeted dose and greater normal tissue sparing, has prompted a re-evaluation of postoperative RT. These advanced techniques require knowledge of the specific patterns of failure after surgery to localize the clinical target volumes at risk. A research published by Baumann et al. in 2012 [45] wanted to identify the pattern of failure within the pelvis after cystectomy and the impact of stage, margin status, nodal status, and number of nodes removed on this pattern. RT should target at least the iliac/obturator nodes in stage ≥pT3 with negative margins; coverage of the presacral nodes and cystectomy bed may be necessary for stage ≥pT3 with positive margins [45].

Bladder-preservation therapy

The relative negative impact on quality of life for urinary diversion and the trend towards organ preservation led many authors to explore the role of conservative management.

Neoadjuvant CT compared with RT or surgery was investigated in an attempt to improve the results of surgery alone or definitive RT maintaining a functioning bladder.

In the European Organization for Research and Treatment of Cancer (EORTC)/Medical Research Council [46] trial, 976 patients undergoing curative cystectomy or radical RT were randomized to receive three cycles of neoadjuvant CT (CDDP, methotrexate and vinblastine (MCV)) in 491 patients or no CT in 485. The absolute difference between groups in 3-year OS of 5.5% (55.5% for CT versus 50% for no CT) was not statistically significant (p=0.075): neoadjuvant CT was associated with a higher pathological CR, but there was no clear evidence on survival. A recent meta-analysis [47] confirmed that neoadjuvant platinum-based combination CT reduces the mortality risk of 13%, with moderate improvement (5%, p=0.016) of 5-year OS, irrespective of the type of local treatment (surgery or RT alone or RT and cystectomy) and without differences between subgroups of patients. There was no evidence to support the use of single-agent platinum. These studies showed that patients treated with RT (conservative approach) have preserved bladder function.

Over the past 15–20 years, several prospective trials investigated conservative therapy in which all patients were treated with transurethral resection of bladder tumors (TURBT) with or without CT followed by CCRT. For patients with CR, a consolidation RT or CCRT regimen was administered. Cystectomy was reserved for incomplete responders or recurrent disease. Many attempts have been made to combine RT (conventional or altered fractionation) with one or more chemotherapeutic agents in order to spare the bladder.

Since 1985, Radiation Therapy Oncology Group (RTOG) trials used a trimodal conservative treatment (TURBT, RT, CT) in patients with T2–T4a muscle invasive bladder cancer, eligible for cystectomy.

In three RTOG trials [48-50], patients were treated with neoadjuvant TURBT and CCRT (conventional or altered fractionation), whereas in two trials [51-52] patients were treated with induction by TURBT with or without CT and CCRT. Cystectomy was reserved for incompletely responders or relapse. In the RTOG 89-03 phase III study, the combination of neoadjuvant CT (MCV for 2 cycles) with CCRT failed to show significant benefits in terms of 5-year local control (61% versus 49%), OS (48% versus 49%) and FFDM (33% versus 39%) compared with CCRT alone, with more toxicity in the MCV arm [52]. In fact, subsequent studies by the RTOG emphasized the impact of adjuvant CT [MCV or CDDP + 5- fluorouracil (FU)] following RT (hypo- or hyperfractionated) [50], with good results at 3 years. Globally, 59%–75% of RTOG patients had CR after 24–40 Gy of CCRT and received an additional boost of 20–25 Gy with concomitant CT. Twenty-five to 40% of patients required a radical cystectomy for incompletely responding or recurrent tumors. The 5-year OS was approximately 50%, with three fourths of those patients achieving a cure for their bladder cancer while maintaining a functioning bladder. Similar results were obtained by the Massachusetts General Hospital with the same schedules [53-54].

Two other important European universities pioneered modern bladder-preservation therapy based on TURBT followed by CCRT. Housset et al. from Paris began a prospective trial of preoperative CT using 5-FU and CDDP with concomitant RT (3 Gy b.i.d., total dose 24 Gy), followed by either cystectomy or additional CCRT. This treatment strategy resulted in a pathological CR of 77% and may be proposed as conservative treatment in patients with a CR to the initial course of CT [55]. These results were supported by the study of Rödel et al. [56], in which 415 patients were treated after TURBT with RT alone (126 patients) or combined with CDDP (240 patients) or CDDP + 5-FU (49 patients), with better CR rates for RT + CDDP – 5-FU (87%) compared with CDDP (66%) or RT alone (61%). Globally, OS at 5 years was 51%.

Similar results were obtained in further series of combined modality treatment for bladder preservation with excellent CR (~70%), and 5-year OS (~50%), with bladder preservation in most cases [48, 49, 53]. Table 2 summarizes the results of these studies [8,40,48–76].

In a recent meta-analysis of fifteen radiation series with different fractionation schedules and total doses, Pos et al. [77]

Series	Pz	Clinical Stage	Induction treatment		pCR(%)	Consolidation CRT regime for complete responders (+/- adjuvant CT)	5-year OS (%)	5-year OS with intact bladder (%)
			Neoadjuvant treatment	Concurrent treatment				
MGH 1986-1993 [53]	106	T2-4a	TURBT, 2 cycles MCV	39.6 Gy at 1.8 Gy + CDDP	66	25.2 Gy at 1.8 Gy+ CDDP	52	43
RTOG 85-12 1986-1988 [48]	42	T2-4a	TURBT	40 Gy at 2 Gy + CDDP	66	24 Gy at 2 Gy+ CDDP	52	42
RTOG 88-02 1988-1990 [51]	91	T2-4a	TURBT, 2 cycles MCV	39.6 Gy at 1.8 Gy + CDDP	75	25.2 Gy at 1.8 Gy+ CDDP	62 (4 years)	48(4 years)
RTOG89-03 1990-1993 [52]	123	T2-4a	TURBT, 2 cycles MCV vs no CT	39.6 Gy at 1.8 Gy + CDDP	61 vs 55	25.2 Gy at 1.8 Gy+ CDDP	49 vs 48	36 vs 40
MGH 1993-1994 [54]	18	T2-4a	TURBT	42.5 Gy at 1.25 and 1.5 Gy b.i.d.+ FU or CDDP	78	22.5 Gy at 1.25 Gy and 1.5 Gy b.i.d. + FU and CDDP (3 cycles MCV adiuvant)	83 (3 years)	78 (3 years)
RTOG 95-06 1995-1997 [49]	34	T2-4a	TURBT	24 Gy at 3 Gy b.i.d. + 5 FU and CDDP	67	20 Gy at 2.5 Gy b.i.d. + FU and CDDP	83 (3years)	66(3 years)
RTOG 97-06 1997-1999 [50]	47	T2-4a	TURBT	40.8 Gy at 1.8 Gy and 1.6 Gy b.i.d.+ CDDP	74	24 Gy at 1.5 Gy b.i.d. + CDDP (3 cycles MCV adiuvant)	61(3 years)	48 (3years)
Russel KJ et al. [57]	34	T1-4	TURBT	44 Gy at 2 Gy + FU	81	16 Gy at 2 Gy + FU	64 (4 years)	NG (overall rate of cystectomy 10 of 34)
Rotman M et al. [58]	20	T1-4	TURBT	60-65 Gy at 1.8 Gy + 5-FU	74		39	NG (19 of 20 maintained bladder)
Orsatti M et al. [59]	76	T1-4	TURBT	40-50 Gy/CDDP-5FU	81		62	45
Given RW et al. [60]	93	T2-4	TURBT, 2 or 3 cycles MVAC or MCV	64.80 Gy at 1.8 Gy fr + CDDP and Docetaxel	63		39	NG
Housset M et al. [55]	120	T2-4	TURBT	24 Gy at 3 Gy + CDDP/FU	77	20Gy at 2.5 Gy/fx + CDDP/FU	63	NG
Varveris H et al. [61]	42	T1-4	TURBT	68-74 Gy at 1.8 Gy + CDDP and Docetaxel	62		78 (median fup 5 months)	NG

Fellin G et al. [62]	56	T2-4	TURBT + 2 cycles MCV	40.8 Gy at 1.8 Gy + CDDP	50	24Gy at 2 Gy/fx + CDDP	55	41
Sauer R et al. [63]	333	T1-4	TURBT	50.4-59 Gy/ CARBO+CDDP	71		56	41
Cervek J et al. [64]	105	T2-4	TURBT, 2-4 cycles MCV		52	50Gy at 2 Gy/fx	58(4 years)	45 (4 years)
Zapatero A et al. [40]	40	T2-4	TURBT+ 3 cycles MCV		70	60Gy at 2 Gy/fx	84(4years)	82.6 (4 years)
Arias F et al. [65]	50	T2-4	TURBT+ 2 cycles MVAC	45 Gy at 1.8 Gy + CDDP	68	20Gy at 2 Gy/fx	48	
Shipley WU et al. [65]	190	T2-4a	TURBT	40 Gy +CDDP	74	25Gy + CDDP	54	45
Rodel C et al. [56]	415	T1-4	TURBT	50.4-59 Gy at 1.8 Gy + CARBO/CDDP (+FU)	72		51	42
Caffo O et al. [67]	16	≥ T2	TURBT	54 Gy/CDDP-Gem	100		NG	NG
Chen WC et al. [68]	23	T3-4	TURBT	60-61.2 Gy at 1.8-2 Gy + CDDP/FU/Leucoverin	89		69 (3 years)	NG
Pejromaure M et al. [69]	43	T2	TURBT	24 at 3 Gy +CDDP/FU	74	2 additional cycles of CRT (dose not given)	60 (specific cancer)	NG 8 overall rate of cystectomy: 25.6 %)
Danesi DT et al. [70]	77	T2-4	TURBT+ 2 cycles MCV (42 pts)	51 Gy at 1 Gy (3fr/day) + CDDP/FU	90	18Gy at 1 Gy (3 fr/day)+ CDDP/FU	58	
Hussain SA et al. [71]	41	T2-4	TURBT	55 Gy at 2.75 Gy + FU and Mitomycin-C	69		36	34 at 50 months (overal rate of cystectomy 12%)
Kragelj B et al. [72]	84	T1-4	TURBT	64 Gy at 1.8-2 Gy + Vinblastine	78		25 (9 years)	NG
Dunst J et al. [73]	68	T2-4	TURBT	50.4-59 Gy at 1.8 Gy+CDDP or Paclitaxel	87		45	NG
James ND et al. [8]	400	T2-4	TURBT					
Koskin PJ et al. [75]	333	T2-4						

Table 2. Series of combined modality treatment for bladder preservation [76].

Abbreviations

CDDP : Cis-diamminedichloroplatinum as Cisplatin
CRT : Chemioradiotherapy
CT : Chemotherapy
MCV : Methotrexate, Cisplatin and Vinblastine
MGH : Massachusetts General Hospital
MVAC : Methotrexate, Vinblastine, Doxorubicin and Cisplatin
NG : Not given
OS : Overall survival
pCR : Pathological Complete Response
TURBT : Transurethral resection of bladder tumors
5-FU : 5- fluorouracil

found evidence for an overall dose–response relationship with an increase in local control by a factor of 1.44–1.47 for an increment in dose of 10 Gy. Hyperfractionated regimens allow an increase in total dose with reduced risk of late complications. A meta-analysis by Stuschke et al. [78] indicated that a hyperfractionated regimen showed an increased OS (odd ratio of death 0.55; p=0.002) and CR (odds ratio of failure 0.44; p=0.001).

Danesi et al. [70] reported the long-term results of a phase I/II trial of CT (MCV) followed by concomitant CDDP + 5-FU and hyperfractionated irradiation (three 100- cGy fractions/day, for a total dose of 69 Gy). In a serie of 77 patients, the complete rate was 90%. The 5-year overall, bladder-intact, tumor-specific, disease-free and cystectomy-free survival rates for all 77 patients were 58.5%, 46.6%, 75%, 53.5% and 76.1%, respectively. Even if accelerated RT may overcome radioresistance due to tumor-cell repopulation, a recent randomized trial [79] reported no improvement of local control or survival rates but an increased acute bowel complications. Hypofractionated schedules have usually been used with palliative intent. There has been only one small phase III study of curative RT in which survival was inferior in the hypofractionated arm [80].

Some trials, in an attempt to improve results, explored the use of new chemotherapeutic agents and accelerated or hyperfractionated RT to increase irradiation dose in combination with CT. New chemotherapeutic agents, in particular gemcitabine and taxanes, are effective in combination with CDDP and RT (paclitaxel and gemcitabine are good radiosensitisers) [61, 74]. A recent Italian study [67] reported the feasibility of a combined scheme with gemcitabine (up to 400 mg/m2) plus CDDP and RT, obtaining 100% CR. Finally, the RTOG 99-06 trial introduced concomitant paclitaxel + CDDP plus bifractionated RT as induction treatment, followed by adjuvant CT (gemcitabine and CDDP) in patients with CR; no specific outcomes are yet available [57].

James ND et al. [8] recently showed, in a phase III randomized trial, very good results with one cycle of neoadjuvant CT and concomitant Mytomicin and 5-FU. This result could be a very good approach and low cost treatment for elderly patients.

Discussion

Quality of life

RT, as an alternative therapy to surgery, could preserve native bladder capacity. The most important symptom after RT is incontinence. Zietman et al. [54] performed urinary dynamic tests and quality of life study in long-term survivors, treated with CRT. Of them 75% had bladder with normal function. Contracted bladder was present only in 2% of pts. Zietman also showed that 54% of men had good erections and 60% were satisfied of their sex life.

Future directions

Through the use of combination therapy with simulators and image-guided RT, administration of radiation therapy it has become more focused [80].

Numerous techniques are being validated and their clinical application clinic seems to be set to grow over the years.

Recent evidence showed that the re-irradiation, using high-precision RT machines, can be used successfully in the treatment of brain metastases, tumors of head and neck, lung, abdominal and pelvic neoplasms, as salvage therapy [81].

Protons can deliver conformal RT, with low effects in organs at risk (OARs) of complications, mainly small and large intestine. Brachytherapy permits to deliver high dose to a small area with sparing of OARs. It should be considered in lesions small and limited. Brachytheraphy was originally made with RADIUM 226, now with Iridium 192 (low dose rate and high dose rate) [82-84].

Hyperthermia is able to improve local control and CR rate (Quadrimodal therapy). Hyperthermia enhances RT induced DNA damage. Important advances in RT are represented by intensity modulated radiotherapy, image guided-radiotherapy and stereotactic RT [85].

Traslational approach

Most recently have been identified markers of response to therapy. Epidermal growth factor receptor (EGFR) positivity seems to be an unfavorable prognostic factor and correlate with DSS and OS in the intact bladder. Also Retinoblastoma protein (Rb) and bcl-2 expression are independent correlates with RT response in muscle infiltrative bladder cancer (MIBC). Also p53 expression and level of apoptosis correlates with treatment response.

There are strongest predictive novel markers for outcome in patients receiving cystectomy or CCRT: patients with tat-interactive protein 60 expression have a significantly longer DSS after cystectomy and patients with expression of meiotic recombination 11 homolog have a better prognosis and a longer DSS after CCRT. [86-87].

Progress goes in the direction of 3D conformal RT combined with CT scans type big bore and novel imaging fusion (Single Photon Emission Computed Tomography, Positron Emission Tomography).

Conclusions

There is a new renaissance of RT in bladder cancer, mainly in conservative approach. RT not necessarily tries to replace surgery, but RT is a good alternative in patients contrary to urinary diversion and in old peoples.

Competing interests

Authors declare no conflict of interest.

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Each author had participated in the work and is responsible for the content.

All authors have interpreted the data. The manuscript was written by Parisi Salvatore and Guglielmi Giuseppe, and all authors have approved the final manuscript.

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