

## Role of external radiation therapy in urinary cancers

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Invasive urinary tumors are relatively rare and their treatment may cause important changes in urinary, sexual, and social functions.

A systematic review of external radiation therapy studies in urinary cancers has been carried out. This synthesis of the literature is based on data from meta-analysis, randomized and prospective trials, and retrospective studies. There are few controlled clinical trials using adjuvant or radical radiotherapy ± chemotherapy in kidney, ureter, and urethra cancers; there are several reports of muscle-invasive bladder cancer using multimodality treatment: intravesical surgery and neo-adjuvant chemotherapy to radiotherapy or concomitant radiochemotherapy with organ preservation.

The conclusions reached for renal cancer are controversial; urethra and ureter cancers data are few and inconclusive; sufficient data now exist in literature to demonstrate that conservative management with organ preservation, for muscle-invasive bladder cancer, is a valid alternative to radical cystectomy, viewed as the gold standard.

**Key words:** chemotherapy, organ preservation, radiotherapy, treatment, urinary cancers

### kidney

Radical nephrectomy remains the only effective therapy for clinically localized renal cancer (RC). However, local recurrence rates are high especially in locally advanced disease. The advantage of external radiation therapy (RT) in RC is controversial. No advantage is demonstrated in patients receiving preoperative irradiation with doses of 20–40 Gy with respect to overall survival (OS) or freedom free of distant metastases (FFDM), although improvement in resectability has been noted. In some early study, postoperative RT have demonstrated an advantage of ~15% on local control (LC) compared with nephrectomy alone, but with inconsistent effect on survival [1].

In a series from Haifa University, postnephrectomy irradiation with a median dose of 46 Gy reduced the rate of local recurrence in patients with stage T3 tumors from 37% (nonirradiated patients) to 10% (irradiated patients) ( $P = 0.05$ ); but in an updated study, postoperative RT did not improve the survival and showed toxicity series [2].

Finally, a recent publication [3] showed 5-year disease-free survival (DFS) of 66% in radiotherapy group and 16% in the no treatment group, with a reduction of local recurrence, and a significant difference in both univariate and multivariate

analyses. No benefit was noted in patients with earlier stage disease.

These series indicated a benefit on LC in patients with high-risk tumors (incomplete resection T3/T4 stage, lymphonode metastases), but no advantage on OS.

In the last years, extracranial stereotactic radiotherapy has been employed in the treatment of primary and metastatic RC, achieving 90%–98% partial response/complete response (CR); this new radiation technique represents a big challenge because side-effects are low and the LC is high due to easy dose escalation [4].

### ureter and urethra

Carcinoma of the ureter and urethra are unusual disease with insufficient clinical experience and the role of RT is not well defined.

Czito et al. [5] reviewed the records of 31 patients with locally advanced transitional cell carcinoma of the renal pelvis and ureter, who underwent surgery followed by adjuvant RT with or without concurrent chemotherapy (CT) [methotrexate, cisplatin (CDDP) and vinblastine (MCV)]. Five-year OS and DFS with adjuvant concurrent chemoradiotherapy (CCRT), with schedules containing CDDP, improved in patients with resected, locally advanced upper tract urothelial malignancies. This regimen should be considered in patients with T3/4 and/or node positive upper tract transitional cell carcinoma.

Retrospective results from Eng et al. [6] of 18 patients with urethral carcinoma showed 44% 5-year OS. Patients with

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advanced cancer treated with surgery alone had a shorter DFS (23.3 months) versus those treated with combination chemo-RT (45.2 months).

Grigsby [7] showed the records of 44 women with carcinoma of the urethra. Treatment was surgery in seven, RT in 25, and combined surgery and RT in 12 patients. The 5-year OS was 42% and the 5-year DFS was 40%.

## bladder

Radical cystectomy with bilateral pelvic lymph node dissection followed by urinary diversion remains the gold standard for treating muscle-invasive bladder cancer and is the single most successful modality reporting long-term OS in the range of 40%–60% [8].

RT is used as single modality treatment, as neo-adjuvant or adjuvant to surgery, or combined by CT with or without conservative local surgery.

### 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, and were younger and in a better general conditions than patients selected for definitive irradiation [1].

In literature, the results are not significant: the 5-year survival for patients treated with RT alone (dose of 60–66 Gy at a 1.8–2 Gy daily fraction) is 32% (range of 22%–50%) [1, 9].

### preoperative RT

The largest experience (338 patients) with preoperative RT obtained pathologic downstaging in 65% of patients and pathological RC in 42%. The 5-year OS was 44%, and the pelvic and distant recurrence were 16% and 43%, respectively [10].

A prospective randomized trial comparing preoperative radiotherapy with exclusive irradiation was conducted by Bloom et al. [11]. The 5-year survival in patients receiving RT followed by cystectomy was 38% versus 29% for those treated with RT alone [not statistically significant (nss)]. There was a significant survival benefit of preoperative irradiation in male patients <60 years of age. Tumor stage reduction and pathological RC were obtained in 49% and in 31% of patients receiving preoperative RT, respectively.

A strong support for the use of preoperative irradiation in patients with T3b bladder cancer was reported by Cole et al. [12]. The 5-year LC in the preoperative group was 91% compared to 72% for those treated with radical cystectomy alone. There was also a benefit in terms of OS and DFS and in FFDM (nss). Tumor doses were 20–50 Gy.

However, a meta-analysis of five randomized trials showed no statistical difference in outcomes between patients treated with preoperative RT and cystectomy alone [13].

Preoperative CCRT showed better results than RT alone. In fact, in the Nordic Cystectomy Trial [14] the combination of

CT (adriamycin + CDDP for two cycles) plus radiotherapy (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 ( $P = 0.03$ ), while no survival benefit was found for early stage disease (T1–T2). In the Canadian randomized study [15], concurrent CDDP improved pelvic disease control with preoperative or definitive RT compared with RT alone ( $P = 0.038$ ). Therefore, some Institutions recommend preoperative RT, with or without CT, for  $T \geq 4$  cm and T3–T4a resectable disease.

### postoperative RT

Postoperative RT is administered in patients with extravesical disease, positive resection margins, or involved pelvic lymph nodes with doses of 40–50 Gy. Some studies reported a reduction of the risk of pelvic recurrence from 30%–50% to 10%–20%, but some patients received also preoperative RT [1]. The main disadvantage of postoperative RT is the high rate (20%–40%) of serious late gastrointestinal complications because of the larger volume of small bowel occupying the pelvis after cystectomy [1, 16].

Patients at high risk of recurrence are probably better treated with CT, which may prevent local and distant relapse and is usually well tolerated.

### bladder preservation therapy

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

Neo-adjuvant CT to RT or surgery was investigated in attempt to improve results of surgery alone or definitive RT maintaining a functioning bladder.

In the European Organization for Research and Treatment of Cancer/Medical Research Council [17] trial, 976 patients undergoing curative cystectomy or radical RT were randomized to receive three cycles of neo-adjuvant CT (MCV) in 491 patients or no CT in 485 patients. The absolute difference between groups in 3-year OS of 5.5% (55.5% for CT versus 50% for no CT) was nss ( $P = 0.075$ ): neo-adjuvant CT was associated with a higher pathological CR, but there was no clear evidence on survival.

A recent meta-analysis [18] confirmed that neo-adjuvant 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 difference between subgroups of patients; there was no evidence to support the use of single-agent platinum.

These studies show that patients treated with RT (conservative approach) have preserved bladder function.

Over the past 15–20 years, several prospective trials investigated conservative therapies in which all patients were treated with transurethral resection of bladder tumor (TURBT)  $\pm$  CT, followed by CCRT. For patients with CR, a consolidation with RT or CCRT regimen was delivered and cystectomy was reserved for incomplete responders or recurrent disease.

**Table 1.** Series of combined modality treatment for bladder preservation

Series	No. of patients	Clinical stage	Induction treatment		pCR (%)	Consolidation CRT regimen for complete responders ( $\pm$ adjuvant chemotherapy)	5-year OS (%)	5-year OS with intact bladder (%)
			Neo-adjuvant treatment	Concurrent treatment				
MGH 1986–1993 [24]	106	T2–4a	TURBT, two cycles MCV	39.6 Gy in 1.8 Gy plus CDDP	66	25.2 Gy in 1.8 Gy plus CDDP	52	43
RTOG 85-12 1986–1988 [19]	42	T2–4a	TURBT	40 Gy in 2 Gy plus CDDP	66	24 Gy in 2 Gy plus CDDP	52	42
RTOG 88-02 1988–1990 [22]	91	T2–4a	TURBT, two cycles MCV	39.6 Gy in 1.8 Gy plus CDDP	75	25.2 Gy in 1.8 Gy plus CDDP	62 (4 years)	44 (4 years)
RTOG 89-03 1990–1993 [23]	123	T2–4a	TURBT, two cycles MCV versus no chemotherapy	39.6 Gy in 1.8 Gy plus CDDP	61 versus 55	25.2 Gy in 1.8 Gy plus CDDP	49 versus 48	36 versus 40
MGH 1993–1994 [25]	18	T2–4a	TURBT	42.5 Gy in 1.25 and 1.5 Gy b.i.d. plus FU and CDDP	78	22.5 Gy in 1.25 and 1.5 Gy b.i.d. plus FU and CDDP (three cycles adjuvant MCV)	83 (3 years)	78 (3 years)
RTOG 95-06 1995–1997 [20]	34	T2–4a	TURBT	24 Gy in 3 Gy b.i.d. plus 5-FU and CDDP	67	20 Gy in 2.5 Gy b.i.d. plus FU and CDDP	83 (3 years)	66 (3 years)
RTOG 97-06 1997–1999 [21]	47	T2–4a	TURBT	40.8 Gy in 1.8 Gy and 1.6 Gy b.i.d. plus CDDP	74	24 Gy in 1.5 Gy b.i.d. plus CDDP (three cycles adjuvant MCV)	61 (3 years)	48 (3 years)
Housset et al. [28]	120	T2–4	TURBT	24 Gy at 3 Gy plus CDDP/FU	77	20 Gy at 2.5 Gy/fx plus CDDP/FU	63	NG
Sauer et al. [29]	333	T1–4	TURBT	50.4–59 Gy/CARBO + CDDP	71		56	41
Shiple et al. [30]	190	T2–T4a	TURBT	40 Gy plus CDDP	74	25 Gy plus CDDP	54	45
Rodel et al. [27]	415	T1–4	TURBT	50.4–59.4 Gy at 1.8 Gy plus CARBO/CDDP (+FU)	72		51	42
Dunst et al. [31]	68	T2–4	TURBT	50.4–59 Gy at 1.8 Gy plus CDDP or paclitaxel	87		45	NG

pCR, pathologic complete response; CRT, chemoradiotherapy; OS, overall survival; MGH, Massachusetts General Hospital; TURBT, transurethral resection of bladder tumor; MCV, methotrexate, cisplatin, vinblastine; CDDP, cisplatin; RTOG, Radiation Therapy Oncology Group; FU, fluorouracil; fx, fraction; NG, not given; CARBO, carboplatin.

Many attempts have been made to combine RT (conventional or altered fractionation) with one or more chemotherapeutic agents in order to bladder sparing.

Since 1985, the Radiation Therapy Oncology Group (RTOG) trials treated, with trimodality conservative treatment (TURBT, RT, CT), 415 patients with T2–T4a muscle-invasive bladder cancer who were candidates to cystectomy.

In three RTOG trials [19–21], patients were treated with neo-adjuvant TURBT and CCRT (conventional or altered fractionation); while, in two trials [22, 23] patients were treated with induction by TURBT ± CT and CCRT; cystectomy is reserved for incompletely responders or relapse.

In the RTOG 89-03 phase III study, the combination of neo-adjuvant CT (MCV × two cycles) with CCRT with CDDP did not show any significant benefit in terms of 5-year LC (61% versus 49%), OS (48% versus 49%), and FFDM (33% versus 39%), compared to CCRT alone, with more toxicity in MCV arm [23]. In fact, the subsequent trials by RTOG pointed out the impact of adjuvant CT [MCV or CDDP + 5-fluorouracil (5-FU)] post-RT (hypo or hyperfractionated) [20, 21], 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. In all, 25%–40% of patients required a radical cystectomy for incompletely responding or recurrent tumors. The 5-year OS was ~50% with 3/4 of those patients achieving a cure for their bladder cancer while maintaining a functioning bladder.

Similar results were obtained by Massachusetts General Hospital (MGH), with the same schedules [24, 25].

Table 1 shows RTOG and MGH studies.

Other two important European University pioneered modern bladder preservation therapy based on TURBT followed by CCRT. Housset et al. [26] from Paris began a prospective trial of preoperative CT using 5-FU and CDDP with concomitant RT (3 Gy b.i.d., total dose of 24 Gy), followed by either cystectomy or additional CCRT. This treatment strategy resulted in pathologic CR of 77% and may be proposed as conservative treatment in patients with a CR to the initial course of chemoradiation. These results were supported by Erlangen experience [27], 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 year was 51%.

Similar results were obtained in further series of combined conservative multimodality treatments with excellent CR (~70%) and 5-year OS (~50%), with preservation of bladder in most patients. Table 1 summarizes the results of these studies.

Salvage cystectomy is used in the case of partial response after induction CCRT treatment (RTOG) or recurrent disease (European trials); in both cases surgery can be curative, reporting a 5-year survival of 50% approximately.

Fractionation and total dose are most important radiation treatment factors for bladder carcinoma.

In a recent meta-analysis, Pos et al. [32] found evidence for an overall dose–response relationship with an increase

in LC by a factor of 1.44–1.47 for an increment in dose of 10 Gy.

A meta-analysis by Stuschke and Thames [33] indicated that hyperfractionated regimen showed an increased OS ( $P = 0.002$ ) and CR ( $P = 0.001$ ).

However, in a recent accelerated RT, randomized trial [34] reported no improvement of LC or survival rates and increasing of acute bowel complications.

Some trials, in attempt to improve results, are exploring the use of new chemotherapeutic agents (gemcitabine and taxanes in combination with CDDP) and accelerated or hyperfractionated RT to increase irradiation dose in combination with CT.

To sum up, the trimodality treatment (TURBT, RT, CT) of invasive bladder cancer may be offered as a valid alternative to radical cystectomy with no diminution in survival related to the delay in cystectomy, the gold standard therapy at present. OS is comparable to recent surgical data, reporting a 5-year OS of ~50%, with bladder preservation in 3/4 of these patients.

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