

Radio-chemotherapy for bladder cancer: Contribution of chemotherapy on local control

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Abstract

The purpose of this study was to review the magnitude of contribution of chemotherapy (CT) in the local control of muscle invasive bladder carcinoma in the studies where a combined radio-chemotherapy (RCT) was used (how much higher local control rates are obtained with RCT compared to RT alone). Studies on radiotherapy (RT) and combined RCT, neo-adjuvant, concurrent, adjuvant or combinations, reported after 1990 were reviewed. The mean complete response (CR) rates were significantly higher for the RCT studies compared to RT-alone studies: 75.9% vs 64.4% (Wilcoxon rank-sum test, $P = 0.001$). Eleven of the included RCT studies involved 2-3 cycles of neo-adjuvant CT, in addition to concurrent RCT. The RCT studies included the one-phase type (where a full dose of RCT was given and then assessment of response and cystectomy for non-responders followed) and the two-phase types (where an assessment of response was undertaken after an initial RCT course, followed 6 wk later by a consolidation RCT for those patients with a CR). CR rates between the two subgroups of RCT studies were 79.6% (one phase) vs 71.6% (two-phase) ($P = 0.015$). The

average achievable tumour control rates, with an acceptable rate of side effects have been around 70%, which may represent a plateau. Further increase in CR response rates demands for new chemotherapeutic agents, targeted therapies, or modified fractionation in various combinations. Quantification of RT and CT contribution to local control using radiobiological modelling in trial designs would enhance the potential for both improved outcomes and the estimation of the potential gain.

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Key words: Bladder; Cancer; Chemoradiotherapy; Local control

Core tip: Chemotherapy is adding approximately an extra 10% to local control rates obtained with radiotherapy alone in the treatment of invasive bladder carcinoma. It seems that potential for radiosensitization by chemotherapy may have reached a plateau. The best achievable tumour control rates, with an acceptable rate of side effects are around 70%. Further increase in complete response rates demands for new combinations, chemotherapeutic agents or modified fractionation.

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INTRODUCTION

In muscle invasive bladder cancer (MIBC) cure can be achieved either with radical radiotherapy (RT) and post-radiation salvage cystectomy or by primary cystectomy

Table 1 The 5-yr overall survival and complete response rates from the University of Erlangen resulting from changes in therapeutic approach over the years^[11-14]

Treatment	Complete response	Overall survival
RT alone	61%	40%
RT + carboplatin	66%	45%
RT + cisplatin	82%	62%
RT + cisplatin + 5-FU	87%	65%

RT: Radiotherapy; 5-FU: 5-fluorouracil.

alone. Seventy percent of patients with bladder cancer are over 60 years of age and co-morbidities may render them unsuitable for high-risk radical surgery. However, although there are no randomized data to compare RT and surgery, similar rates of cause-specific survival are reported: about 50% at 5 years^[1].

In an attempt to further improve the results of the non-surgical approach various combinations of RT with chemotherapy (CT) have been used for the treatment of MIBC; for instance, addition of neoadjuvant chemotherapy to surgery or RT improves 5-year survival rates by 5%-8%^[2,3]. Quantification of the contribution of CT to local control rates has been attempted for other neoplasms^[4]. Trimodality treatment, involving transurethral resection of the bladder tumor (TURBT) and RT in various sequencing combinations with CT, has been shown to produce 5-year and 10-year overall survival rates comparable to those of radical cystectomy. The current 5-year overall survival rates range from 50% to 67% with trimodality treatment, and approximately 75% of the surviving patients maintain their bladder. After trimodality treatment, complete response is obtained in about 70% of patients with muscle-invasive bladder cancer.

Local control as the main prognostic factor for survival rates, is the reported outcome parameter in the majority of studies and we therefore reviewed the local control rates reported from randomized controlled trials comparing RT-alone with RT combined with CT or from non-randomized studies reporting results of combined RT and CT, in an attempt to determine the current status of complete response rates with combined RT and CT and quantify the contribution of CT to local control.

The purpose of current study was to review the relevant literature and record the reported LC rates in various studies, so as a quantification of the contribution of CT on local control rates would be possible, using the methods of clinical radiobiology^[4] (this work will follow shortly). As a result we didn't make a particular recording and analysis of the toxicity of RCT studies, although we made a literature-based comment at the end of the "Results" section.

We reviewed studies on RT and combined RCT (neo-adjuvant, concurrent, adjuvant or combinations) reported after 1990, so that treatment conditions and equipment would be closer to currently available tech-

niques. We searched MEDLINE and PUBMED using combinations of terms such as bladder carcinoma, trimodality therapy, organ preservation, radical cystectomy, chemotherapy, radiotherapy, TURBT and radiochemotherapy. We also took into account studies included in the relevant recent reviews^[5,6] and COHRANE Collaboration. Studies with inadequate information and reporting on patient eligibility criteria, treatment methods, doses and fractionation of RT and CT, response rates and survival times were excluded.

RESULTS OF STUDIES REVIEW

Radiochemotherapy studies

The centres that pioneered bladder preservation therapy were Harvard University^[7-9], the University of Paris^[10] and the University of Erlangen^[11-14]. In protocols developed at Harvard and Paris, patients for bladder preservation are selected according to their response after induction RCT and only patients who have had a complete response (CR) undergo consolidative RCT for bladder preservation, whereas non-CR patients undergo radical cystectomy. These schemes place priority on cancer control by carrying out salvage cystectomy with minimal delay for non-responders. In addition, a lower dose of preoperative irradiation would also reduce the risk of complications.

In the Erlangen protocol^[11-14] patients receive full-dose CT + RT and then are evaluated for therapeutic response; non-CR patients then undergo cystectomy. This approach of initial full dose RT and CT allows more time for a response to be demonstrated and may add some more complete responses (compared with the above-mentioned two-phase treatment). The Erlangen experience covers a span of more than 20 years. In their initial work, RT was given alone; since 1985, chemotherapy has been given concomitantly with RT. The first chemotherapeutic agent used was carboplatin, later on replaced by cisplatin. Finally 5-fluorouracil (5-Fu) was added to cisplatin. The complete response and the 5-year overall survival rates improved with each change (Table 1).

Another major difference between the above protocols lays with the RT fractionation schemes. Erlangen used a standard fractionation scheme, Paris uses a bifractionated split course and the Boston group has used several protocols (Tables 1 and 2), changing fractionation schemes over the years.

Important results are recently reported from the University of Birmingham team and the BC2001 study^[15]. In this multicenter, phase-III trial, 360 patients with MIBC were randomly assigned to undergo RT with or without synchronous chemotherapy. The regimen consisted of fluorouracil on days 1-5 and 16-20 of the RT schedule and mitomycin-C on day 1. After a median follow up of more than 5 years they reported two-year locoregional disease-free survival rates of 67% in the chemoradiotherapy group and 54% in the RT group; these figures are taken as the CR rates. RT dose and fractionation

Table 2 Series of trimodality bladder-sparing treatment for muscle-invasive bladder cancer

Study	No. of patients	A' phase	CR	B' phase 6 wk later
RTOG 85-12 ^[17]	42	TURBT, 20 × 2 Gy = 40 Gy + CDDP	66%	12 × 2 = 24 Gy + CDDP
RTOG 88-02 ^[18]	91	TURBT, NACT 2 × MCV, 22 × 1.8 = 39.6 Gy + CDDP	75%	14 × 1.8 = 25.2 Gy + CDDP
RTOG 89-03 ^[8]	123	TURBT, NACT 2 × MCV <i>vs</i> no NACT-22 × 1.8 = 39.6 Gy + CDDP	61% <i>vs</i> 55%	14 × 1.8 = 25.2 Gy + CDDP
RTOG 95-06 ^[19]	34	TURBT, (3 Gy × 2 per day) × 4 = 24 Gy + 5-FU/CDDP	67%	(2.5 Gy × 2 per day) × 4 = 20 Gy + 5-FU/CDDP
RTOG 97-06 ^[20]	47	TURBT, (1.8 Gy + 1.6 Gy per day) × 12 = 40.8 Gy + CDDP	74%	(1.5 × 2 per day) × 8 = 24 Gy + CDDP→ACT 3MCV ¹
RTOG 99-06 ^[21]	80	(1.6 + 1.5 per day) × 13 d = 40.3 + CDDP/paclitaxel	81%	(1.5 × 2 per day) × 8 = 24 Gy + CDDP/paclitaxel
Housset <i>et al</i> ^[10]	54	(3 Gy × 2 per day) × 4 = 24 Gy + CDDP/5-FU	74%	(2.5 Gy × 2 per day) × 4 = 20 Gy + CDDP/5-FU
Given <i>et al</i> ^[22]	93	NACT 2-3 × MVAC/MCV→36 × 1.8 = 64.8 Gy + CDDP	63%	
Fellin <i>et al</i> ^[23]	56	NACT 2 × MCV→20 × 2 = 40 Gy + CDDP	50%	12 × 2 = 24 Gy + CDDP
Kachnic <i>et al</i> ^[24]	106	TURBT, NACT 2 × MCV→RCT: 25 × 1.8 = 45 Gy + CDDP	66%	11 × 1.8 = 19.8 Gy + CDDP
Arias <i>et al</i> ^[25]	50	TURBT, NACT 2 × MVAC→25 × 1.8 = 45 Gy + CDDP	68%	10 × 2 = 20 Gy
Zapatero <i>et al</i> ^[26]	40	TURBT, NACT 3 × MCV→30 × 2 = 60 Gy	70%	
Chen <i>et al</i> ^[27]	23	TURBT, 30 × 2 = 60 Gy or 34 × 1.8 Gy = 61.2 Gy + CDDP/FU/leucovorin	89%	
Peyromaure <i>et al</i> ^[28]	43	TURBT, (3 Gy × 2 per day) × 4 = 24 Gy + CDDP/FU	74%	(3 Gy × 2 per day) × 4 = 24 Gy + CDDP/FU
Danesi <i>et al</i> ^[29]	77	NACT 2 × MCV→(3 × 1 Gy per day) × 23 = 69 Gy or (2 × 1.5 Gy per day) × 23 = 69 Gy	90%	
George <i>et al</i> ^[30]	60	NACT 2 × MVAC/MCV→65 Gy (median dose) + CDDP/carbo/5-FU	75%	
Kragelj <i>et al</i> ^[31]	84	32 × 2 = 64 Gy + concurrent vinblastine	78%	
Cobo <i>et al</i> ^[32]	29	NACT 2 × MCV/GC→25 × 1.8 = 45 Gy + CDDP	86%	4 wk later: RT-alone 11 × 1.8 Gy = 19.8 Gy
Perdonà <i>et al</i> ^[33]	43	NACT 2 × MCV→median dose 65 Gy standard fractionation	74.40%	
Perdonà <i>et al</i> ^[33]	78	NACT 2 × MCV→median dose 65 Gy standard fractionation + CDDP	89.70%	
Gamal El-Deen <i>et al</i> ^[34]	186	None <i>vs</i> NACT 2 × MCV/MVAC/GC→25 × 1.8 = 45 Gy + CDDP	81.60%	11 × 1.8 Gy = 19.8 Gy + the same chemo
Sabaa <i>et al</i> ^[35]	104	NACT 3 × GC→20 × 2 = 40 Gy + CDDP	78.80%	10 × 2 = 20 Gy + CDDP
Gogna <i>et al</i> ^[36]	113	32 × 2 = 64 Gy RT + CDDP	70%	
Choudhury <i>et al</i> ^[37]	50	20 × 2.625 = 52.5 weekly Gemcitabine	88%	
James <i>et al</i> ^[15]	71	20 × 2.75 Gy = 55 Gy + mitomycin C and 5-FU or	80.7% ³	
Coppin <i>et al</i> ^[16]	111 RT/CT arm	32 × 2 Gy = 64 + mitomycin C and 5-FU		
Sauer <i>et al</i> ^[11]	51 RT/CT-arm	30 × 2 Gy = 60 Gy with CDDP	47%	
Rödel <i>et al</i> ^[12]	95	50.4-59.4 Gy at 1.8 Gy plus carboplatin	66%	
Weiss <i>et al</i> ^[13]				
Ott <i>et al</i> ^[14]				
Sauer <i>et al</i> ^[11]	145	50.4-59.4 Gy at 1.8 Gy plus cisplatin	82%	
Rödel <i>et al</i> ^[12]				
Weiss <i>et al</i> ^[13]				
Ott <i>et al</i> ^[14]				
Sauer <i>et al</i> ^[11]	49	50.4-59.4 Gy at 1.8 Gy plus Cisplatin/5-FU	87%	
Rödel <i>et al</i> ^[12]				
Weiss <i>et al</i> ^[13]				
Ott <i>et al</i> ^[14]				

¹Number of fractions in RT or number of cycles in chemotherapy; ²In this study neoadjuvant CT followed by RT was compared to neoadjuvant CT followed by combined RCT (radio-chemotherapy); ³Calculated from Kaplan-Meier curves. CDDP: Cisplatin; 5-FU: 5-fluorouracil; MCV: Methotrexate, cisplatin and vinblastine; GC: Gemcitabine-Cisplatin; CR: Complete response; TURBT: Transurethral resection of bladder tumor; RT: Radiotherapy; CT: Chemotherapy; NACT: Neoadjuvant CT; ACT: Adjuvant CT; RTOG: Radiation therapy oncology group; MVAC: Methotrexate, vinblastine, doxorubicin and cisplatin.

schedules were 64 Gy in 32 fractions and 55 Gy in 20 fractions.

Finally, in a study organized by the National Cancer Institute of Canada RT alone was compared with concomitant RCT (cisplatin)^[16], with the latter regime demonstrating an improved local control rate. In that trial patients were randomized to a preoperative dose of RT with or without cisplatin. A radical cystectomy or a RT boost to the bladder was then performed following a non-randomized allocation. In patients who opted

for conservative treatment, CR at cystoscopy after the induction phase and bladder preservation rate at last follow-up were higher in the combined arm. Of patients who were randomized to the combined arm and who underwent a cystectomy, 54% presented no evidence of invasive disease in the removed bladder, as compared with 40% in the RT alone arm.

Although there are many studies reporting on combined RCT (Table 2) there are only a few randomized controlled trials comparing directly RT *vs* RCT.

It is worth mentioning the Radiation Therapy Oncology Group (RTOG) studies organized between 1990 and 2002 which although not randomized have offered further perspectives to the combined modality treatments of MIBC. The prospective RTOG studies 8512, 8802, 8903, 9506, 9706, 9906 enrolled patients who underwent combined-modality therapy.

RTOG 85-12 protocol^[17] was the first trial developed. 42 patients with invasive bladder cancer, clinical Stages T2-4 were treated with pelvic RT 40 Gy in 4 wk and cisplatin 100 mg/m² on days 1 and 22. Complete responders were given an additional 24 Gy bladder boost plus a third dose of cisplatin; patients with residual tumor after 40 Gy were assigned radical cystectomy. Encouraging results of this first study led to several others.

The RTOG 88-02 protocol^[18], was a phase II trial that evaluated the toxicity of adding neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) to the combined treatment. Ninety-one enrolled patients received two courses of methotrexate, cisplatin, and vinblastine (MCV regimen) followed by RT with 39.6 Gy and concurrent cisplatin. After complete urologic evaluation, operable patients who achieved complete response were selected for bladder preservation and treated with consolidation cisplatin-RT. Treatment was well tolerated, and a randomized phase III trial followed (RTOG 89-03) to assess the efficacy of neoadjuvant MCV.

RTOG 89-03^[8]: Between 1990 and 1993, 123 patients were randomly assigned to receive or not, two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine before 39.6-Gy pelvic RT with concurrent cisplatin in two courses, 3 wk apart. Patients who achieved a clinical CR received consolidation therapy with 25.2 Gy of additional RT (total dose 64.8 Gy) and one additional course of cisplatin. The addition of neoadjuvant MCV chemotherapy, did not show any benefit in terms of complete response rate, overall survival, or bladder preservation rate, and so the strategy was abandoned.

RTOG 95-06^[19]: Between 1995 and 1997, 34 eligible patients were entered onto RTOG phase I / II protocol 95-06. After TURBT, patients were treated with induction chemoradiotherapy consisting of cisplatin and fluorouracil combined with RT using twice-daily 3-Gy fractions to the pelvis for a total dose of 24 Gy. Patients who achieved a clinical CR received consolidation therapy with the same chemotherapy and 20 Gy of additional RT to the bladder given in twice-daily 2.5-Gy fractions (total dose 44 Gy to bladder and tumor, 24 Gy to pelvic lymph nodes).

RTOG 97-06^[20]: Between 1997 and 1999, 47 eligible patients were entered on RTOG phase I / II protocol 97-06. After TURBT, induction therapy involved 13 d of concomitant boost RT, 1.8 Gy to the pelvis in the morning followed by 1.6 Gy to the tumor 4 to 6 h later (40.8 Gy to bladder tumor and 21.6 Gy to regional lymph nodes). For sensitization, cisplatin was given on the first 3 d of each treatment week. Patients having achieved a CR, were treated with consolidation chemoradiotherapy consisting of 1.5 Gy pelvic RT delivered twice-daily

to 24 Gy (total dose 64.8 Gy to bladder, 45.6 to pelvic lymph nodes) with sensitizing cisplatin. Adjuvant CT followed with methotrexate, cisplatin, and vinblastine.

RTOG 99-06^[21]: Between 1999 and 2002, 81 eligible patients were entered on RTOG phase I / II protocol 99-06. After TURBT, induction therapy involved 13 d of concomitant boost RT, 1.6 Gy to the pelvis in the morning followed by 1.5 Gy to the bladder for the first five sessions (7.5 Gy) then to the tumor for eight sessions (12.0 Gy) in the afternoon (20.8 Gy to pelvis, 28.3 to the whole bladder, and 40.3 Gy to the bladder tumor). Weekly cisplatin and paclitaxel were included as radiation sensitizers. Patients who achieved a clinical CR received consolidation chemoradiotherapy consisting of 1.5 Gy pelvic RT delivered twice-daily to 24 Gy (total dose 64.3 Gy to tumor volume and 44.8 Gy to pelvic lymph nodes) with the same chemotherapy, followed by adjuvant gemcitabine and cisplatin. Other studies please see Table 2^[22-37].

Radiotherapy-alone studies

For the purpose of current presentation we also reviewed the RT-alone studies and those studies of the last 20 years properly reported and documented were included (see above selection of RT/CT studies^[38-46]). RT-alone has been traditionally an option mainly for those who were not medically fit to have a cystectomy.

Toxicity of radiochemotherapy and quality of life

The addition of CT to RT is adding haematologic toxicity. Efstathiou *et al.*^[47] from Massachusetts General Hospital (MGH) have reported five hematologic/infectious deaths of patients following chemotherapy and one death from cardiopulmonary arrest following cystectomy in patients treated at MGH in the context of clinical trials between in the years 1986-2006. However RCT is generally reported as tolerated by the patients. Transient cystitis and enteritis are usually managed symptomatically during treatment and the symptoms typically resolve within 3 wk after completion of CRT.

As regards late toxicity, 5%-10% of patients are generally reported with genitourinary and gastrointestinal toxicity. Very few patients had severe bladder toxicity requiring radical cystectomy; none of the 348 patients at Harvard University and just three of 186 patients at Erlangen University required RC for bladder morbidity^[12,47].

After bladder preservation through trimodality therapy, most patients maintain a good quality of life (QoL) with a better sexual function compared to radical cystectomy^[6,47]. According to a QoL and urodynamic study from Harvard University, three-quarters of bladder-preserved patients retained compliant bladders with normal capacity and flow values, 85% of them reported no or only mild bladder symptoms, half the men reported normal erectile function, and only one-fifth had mild to moderate bowel symptoms^[6,48].

Summary of studies

Table 1 summarises the systematic improvements re-

Table 3 Local control rates after external beam radiotherapy-alone for different dose and fractionation schedules

Study	No. of patients	RT fractionation schedule	CR rate
Gospodarowicz <i>et al</i> ^[38]	254	15 × 2.33 Gy + 5 × 3 Gy	57%
Cowan <i>et al</i> ^[39]	60	20 × 2.63 Gy = 52.5	75%
Cowan <i>et al</i> ^[39]	45	16 × 3.44 = 55 Gy	71%
Cowan <i>et al</i> ^[39]	44	20 × 2.88 = 57.5 Gy	80%
Pos <i>et al</i> ^[40]	50	20 × 2.75 Gy = 55	74%
Scholten <i>et al</i> ^[41]	123	6 × 6 = 36 Gy (1 fraction per week)	44%
Shipley <i>et al</i> ^[7]	58	36 × 1.8 = 65 Gy	56%
De Neve <i>et al</i> ^[42]	67	33 × 2 = 66 Gy	55%
Yavuz <i>et al</i> ^[43]	87	(25 × 1.8) + (15 × 1.5 as a second fraction per day the last 3 wk) = 67.5 Gy	64%
Borgaokar <i>et al</i> ^[44]	163	20 × 2.625 = 52.5 Gy	61%
James <i>et al</i> ^[15]	71	20 × 2.75 Gy = 55 Gy	69.70%
	106	32 × 2 Gy = 64	
Coppin <i>et al</i> ^[16]	48, RT-alone arm	30 × 2 Gy = 60 Gy	31%
Sauer <i>et al</i> ^[11]	126	50.4-59.4 Gy at 1.8 Gy	61%
Rödel <i>et al</i> ^[12]			
Weiss <i>et al</i> ^[13]			
Ott <i>et al</i> ^[14]			
Edsmyr <i>et al</i> ^{[45]1,2}	85	32 × 2 = 64 Gy (in 8 wk) 2 wk rest after half of total dose	36%
	83	(3 × 1 Gy per day) × 28 = 84 Gy (in 8 wk) 3 fractions per day, 4 h apart	59%
Gobolenko <i>et al</i> ^{[46]1,2}	43	30 × 2 = 60 Gy, (in 8 wk)	16%
²	26	2 × 1 Gy per day × 30 = 60 Gy, (in 8 wk)	23%
²	61	(2 × 1 Gy per day) × 35 = 70 Gy (in 9 wk)	34%
²	47	(2 × 1.2 Gy per day) × 28 = 67.2 Gy (in 7.5 wk)	23%

¹In those two randomized studies hyperfractionation was used with a high total dose and resulted in a significantly superior complete response (CR) and survival. However they were not included in our analysis as they were conducted in 70 s and 80 s (see "Methods and Material"); ²The studies below were not included in the present analysis. They are presented to show the advantage of hyperfractionated radiotherapy (RT)-schedules and the higher biologically effective dose delivered.

ported by the Erlangen group in moving from RT alone to RT plus concurrent cisplatin or 5-FU. In Table 2 the trimodality studies and in Table 3 the RT-alone studies are summarised.

It is important to note that the mean CR rates were significantly higher for the RCT studies 75.9% *vs* 64.4% for the RT-alone studies (Wilcoxon rank-sum test, $P = 0.001$).

It needs to be re-iterated that the RCT studies included the one-phase type (where a full dose of RCT was given and then assessment of response and cystectomy for non-responders followed) and the two-phase types (where an assessment of response was undertaken after an initial RCT course, followed 6 wk later by a consolidation RCT for those patients with a CR). CR rates between the two subgroups of RCT studies were 79.6% (one phase) *vs* 71.6% (two-phase) ($P = 0.015$).

DISCUSSION

Mean CR rates were higher for RCT studies compared to RT-alone. In reality 11 of the included studies (Table 2) involved 2-3 cycles of neo-adjuvant CT, in addition to concurrent RCT. This may result in an additional effect of neo-adjuvant CT. The neo-adjuvant CT would be expected to shrink the tumour size prior to administration of the main component of treatment, meaning that it would be easier to establish good LC irrespective of the precise chemotherapy contribution to the subsequent RCT schedule. Although individual studies were unable

to confirm improved results of neo-adjuvant CT, meta-analyses have made this possible^[3].

Other subgroups of studies were those of one- and two-phase RCT schedules. CR rates between the two subgroups of RCT studies were 79.6% (one phase) *vs* 71.6% (two-phase) ($P = 0.015$). This difference of 8% certainly calculated from small numbers of studies, may account for the tumours with a delayed response which did not have enough time to show a CR after the first phase of the two-phase treatments. In the two-phase studies there was a time of approximately 6 wk between the first and the second (consolidation) phase of treatment, to allow for cystoscopic assessment of the response of the tumor to RCT. This may also have induced some repopulation of bladder tumors that would potentially compromise local control rates. Which of the two above-mentioned factors is mainly contributing to this 8% difference is not possible to know. Moreover in most of the above studies a course of neo-adjuvant CT was used, which again has a confounding influence on the findings.

As expected the recorded studies were characterized by inhomogeneous treatment protocols mainly due to variations in: (1) CT-RT sequencing; (2) the stage and extent of the disease; (3) patients performance status; (4) the extend of TURBT; (5) lymphovascular space invasion; (6) haemoglobin, serum C-reactive protein level; (7) epidermal growth factor receptor expression and Her2/ NF- κ B expression^[6]; (8) RT fractionation; and (9) the overall treatment time of RT protocols.

A retrospective analysis by Majewski *et al.*^[49] has shown a weak and not statistically significant relationship between the overall treatment time and CR rate, suggestive of a low repopulation rate (which we have assumed to be 0.2 Gy/d following a time lag of 28 d) compared with squamous-cell carcinomas of head and neck, lung, *etc.* (where it has been calculated as being as high as 0.9 Gy/d. In addition, Horwich *et al.*^[50] have reported that their accelerated schedule did not improve local control or survival rates and was associated with increased complications.

The impact of RT fractionation on local tumour control has been reported in a few studies. In a recent analysis of 15 radiation series with different fractionation schedules and total doses (five combined with brachytherapy), Pos *et al.*^[51] found that after an increase in total dose of 10 Gy, the odds of local control at 3 years increase by a factor of 1.44 (95%CI: 1.23-1.70) for external beam of RT. This indicates that a RT dose escalation could significantly improve local control. Hyperfractionated regimens allow for an increase in total dose with no increase in the risk of late complications (Table 3).

It is evident from the present analysis that the best achievable tumour control rates, with an acceptable rate of side effects is around 70%. Potential for radiosensitization by CT may have also reached a plateau. In an attempt to increase the radiosensitivity without increasing toxicity, especially for elderly patients, various methods have been or are being investigated.

Concurrent capecitabine, paclitaxel^[15] or gemcitabine^[37], modification of tumour hypoxia^[52], hyperthermia along with RT^[53,54]. Future aspects of radiosensitization relate to the potential inhibition of oncogene products frequently activated and overexpressed in bladder cancer, such as H-ras and c-erbB1^[55]. A randomized RTOG trial (RTOG 05-24) uses chemoradiotherapy with paclitaxel and trastuzumab for Her-2-overexpressing tumors, whereas the control group receive RT with weekly paclitaxel but not trastuzumab. Other treatments are being investigated by RTOG: *e.g.*, trials 02-33, 07-12, 09-26.

Further increase in CR response rates demands for new combinations, chemotherapeutic agents or modified fractionation. Improved analysis of the quantification of CT contributions to LC of MIBC, might be helpful in the design of clinical protocols or trials. The inclusion of radiobiological modelling and linear-quadratic isoeffective formula^[56-59] in trial designs would enhance the potential for both improved outcomes and the estimation of the potential gain^[60,61]. Such a radiobiological modelling analysis similar to that published for cervical cancer^[4], will follow for muscle invasive bladder carcinomas.

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