12. **Urinary Bladder Cancer**

Introduction

Next to prostate carcinoma, urinary bladder cancer is the most common malignant urologic tumour in Sweden. About 2 000 new cases are diagnosed every year, predominantly in elderly men. The male: female ratio is about 3:1 and the mean age at diagnosis is 70 years. The mortality of bladder cancer is approximately 600 cases per year.

The incidence increased significantly with 1.2 per cent per year for men and 0.9 per cent per year for women during 1977–96 but has changed only slightly since then. The 5-year relative survival increased from 60 per cent to 71 per cent between 1960 and 1986, most of the increase occurring during the 60s. Since then there is no significant improvement in survival.

Bladder cancer is more frequent in urban than in rural areas. This is most likely explained by environmental factors. Occupational exposure to carcinogens contributes to approximately 25 per cent of cases. The most important single risk factor is cigarette smoking, which is believed to contribute to almost 50 per cent of the carcinomas in men and at least 30 per cent of those in women.

Urothelial cancers are grouped according to the TNM-staging system (1997) into superficial (Ta,Tis,T1), muscle invasive (>T1) and metastatic disease, Table 1.

Table 1 *Staging System for Bladder Cancer (TNM-Classification 1997).*

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carconioma
Tis	Carcinomia in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical fat
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate or uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
Lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in a single lymph node, 2 cm or less in greatest dimension
N2	Metastases in a single lymph node, more than 2 cm, but not more than 5 cm, in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastases in a single lymph node more than 5 cm in greatest dimension
Distant metastases (M)	
MX	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Clinical behaviour and prognosis depend on tumour stage, which forms the basis for the primary treatment. Histopathologic grading is presently made mainly according to the WHO classification of 1973 but the modified WHO classification according to Bergqvist and Moberger is also used by some centres [4]. A modified grading system, WHO 1999, was recently proposed by uro-pathologists to further increase the accuracy of the grading procedure.

Superficial tumours represent about 70 per cent of newly detected cases. Recurrences or a new occurrence of urothelial carcinomas are found in 50–70 per cent of the patients within five years after the initial endoscopic resection. The risk of progression to higher stages is low. The primary

therapeutic aim in superficial urothelial cancer is to prevent recurrences and future progression.

The survival of patients with Ta tumours is high with a relative survival of 95 per cent or more at five years but decreases significantly in T1 tumours.

T1 tumours are characterized by invasion of the lamina propria. Approximately 25 per cent of the cases are associated with Tis. Recurrence rates are as high as 50 per cent by one year, 80 per cent by three years and 90 per cent within five years. About 50 per cent of poorly differentiated tumours (T1G3) are reported to develop muscle invasive disease within five years with an even higher risk in case of concomitant Tis.

Once invasion of the muscle layer (T2–T4) has occurred the patients are at a high risk of developing regional nodal and subsequent distant metastases. About 20–25 per cent of bladder cancer patients have muscle invasive disease at diagnosis.

The 5-year survival rate in non-metastatic, muscle invasive bladder cancer is 40–50 per cent for clinical stage T2 disease and approximately 25–35 per cent in cancer with extravesical extension (T3). Invasion of the prostate gland (T4a), or fixation to the pelvic wall confers an even worse prognosis [15,21,38].

The treatment of bladder cancer ranges from transurethral resection in superficial tumours to radical cystectomy with lymph node dissection in muscle invasive disease. Transurethral resection with or without random biopsies is used for staging of bladder cancer but also as a therapeutic procedure. Following transurethral resection intravesical chemo- or immunotherapy (BCG) may be used as additional treatment in selected patients such as those with Tis, T1 or multiple and recurrent superficial tumours. These treatments were recently reviewed in the SBU-report about the use of chemotherapy [34]. Radical cystectomy with urinary diversion is performed in patients with locally aggressive tumours, predominantly in cases with muscle invasion. Systemic chemotherapy may be indicated together with radical cystectomy or for the treatment of advanced cases with or without metastatic spread [34]. Radiation therapy (RT) may be used for cure of locally advanced bladder cancer or for palliation. Bladder preservation by intense chemoradiotherapy after

extensive transurethral resection is a new, promising treatment with reported similar 5-year survival rates as cystectomy [34]. The ideal treatment for muscle invasive bladder cancer would be bladder-preserving therapy with a well functioning bladder and total eradication of the tumour without compromising survival.

Most of the patients who succumb to bladder cancer die from metastatic disease within two years without any signs of local recurrence. The most common metastatic sites are regional lymph nodes, lungs, liver and bone. The survival of patients with bladder cancer has not improved significantly during the past decades. Distant metastases in patients without any signs of local recurrence after radical cystectomy indicates the presence of subclinical metastases already at the time of diagnosis. Other treatment modalities such as chemotherapy in addition to radical surgery or radiotherapy are needed to counteract existing subclinical metastatic disease at the time of the primary treatment.

Assessment of new literature

Search method and selection

Search for literature was made in Medline for the period 1966–October 2001 with the use of the key words (MeSH): "bladder neoplasms" in combination with "radiotherapy" as subheading, MeSH or text. The search was primarily confined to randomized controlled studies (RCT). For the period 1990–October 2001 further search included meta-analysis, systematic overviews, prospective studies, case-control studies and cohort studies with the exclusion of letters, editorials and case-reports. Additional search was made in the Cochrane Library.

A total number of 317 references were retrieved. Fiftyeight references (RCT) were retrieved during 1966–1989, and 51 (RCT) during 1990–October 2001. The extended search 1990–October 2001 on prospective, case-control and cohort studies retrieved 208 references.

Abstracts from all papers were reviewed. Reprints of all 109 RCT studies between 1966 and October 2001 were evaluated.

Reasons for exclusion of publications not further analysed were:

A Not randomized controlled studies.
B Reports on patients with cancer in the bilharzial bladder.
C RCT studies on neo-adjuvant, concomitant and adjuvant chemotherapy in muscle invasive bladder cancer were not reviewed further since this issue has been evaluated in the recent SBU chemotherapy report (SBU 155/1) [34].
D Reports considered not being relevant to this report
E Studies with fewer than total 50 patients were not further reviewed for treatment efficacy. Regarding evaluation of side-effects reports with less than 50 patients were accepted.

The remaining 33 articles were listed in overviews and form the base for the conclusions in this report.

Overview of new studies

Radiotherapy as definitive treatment – radiation dose, fractionation, schedule

Overview 1 (after the list of references)

Dose per fraction

Most of the experience in humans is based on a fractionation schedule with 2 grays (Gy) per fraction, one fraction per day, which is considered to be the standard fractionation. The possible benefit of either increased or decreased dose per fraction has been investigated in a few studies. Increased dose per fraction gives higher "biological dose efficacy" (BED), saves time on treatment machines, but entails risk of higher toxicity unless the total dose is decreased. The terapeutic index probably decreases with higher doses per fraction, even if the total dose is lowered. Lower dose per fraction is considered to protect normal tissues from radiation side-effects and a higher total dose might be given.

Three randomized studies have been performed [19,20,39].

Hyperfractionation

In hyperfractionated radiotherapy (HRT) the number of fractions per day are increased but a smaller dose per fraction is given. The total dose is often increased during the same treatment time. The aim of HRT is to increase tumour control by increasing the total dose, while keeping severe late side effects on the same level. Smaller dose per fraction is also considered to increase the irradiation efficacy on hypoxic tumour cells.

Two randomized studies were found comparing conventional fractionation with hyperfractionation [17,23]. One of the studies [17] was reanalysed after 10 years follow-up [32].

Side-effects have been evaluated in two studies [11,17]. In one of them [17], major side-effects of the bowel requiring surgical treatment were reported in 10/83 patients treated to 84 Gy with 3 fractions per day, in comparison to 4/85 treated to 64 Gy, one fraction per day. The difference in bowel side-effects did not reach statistical significance. The hyperfractionated group was treated with an interval of four hours between the fractions. A separation of four hours between each fraction has later been shown to be the minimum time needed between fractions to get adequate repair in normal tissues. Today, a six hour span between fractions is often recommended.

Split-course

The use of continuous versus split course radiotherapy has both radiobiological and patient tolerance reasons. Initially it was hypothesised that the rest-period would allow repair of normal tissue damage, decrease morbidity and increase oxygenation of tumour cells. However, later studies have suggested, in some tumour types, that tumour cell repopulation during the split period decreases local control [22]. It has been suggested, though, that repopulation in bladder cancer starts late (5–6 weeks) [28]. Split-course radiotherapy has been compared to continuous radiotherapy in 3 randomized trials [24,27,29]. In two of the trials, a hypofractionation was also performed, which complicates the evaluations.

The literature shows that:

- Higher dose per fraction to the same total dose might increase efficacy, but also increases the risk of more severe toxicity.
- Hyperfractionated radiotherapy of bladder cancer improves local control and increases overall survival. The results are sustained at 10 year follow-up.
- Hyperfractionated radiotherapy might increase acute and late side-effects if the interval between the treatments is only four hours.
- Split-course radiotherapy (2–4 weeks split) was as efficient as continuous radiotherapy regarding survival and local control. There was no difference in late side effects.

	1 = High	2 = Moderate	3 = Low	Total*
M	–	1/(345)	–	**1**
RCT	–	3/493	6/557	**9/1 050**
Total	**–**	**4/493**	**6/557**	**10/1 050**

*) In the figures within brackets all patients reported in the individual articles are counted. Many patients are reported in more than one article and the figures without brackets indicate number of patients only counted once.

Radiotherapy with photons versus radiotherapy with neutrons

Overview 2 (after the list of references)

The rationale for high linear energy transfer, LET, radiation (e.g. treatment with neutrons) is its lower Oxygen Enhancement Ratio (less dependent on oxygen concentration), decreased repair and less dependence on cell cycle phase. The facilities for photon therapy used during the 1980s, when the randomized studies evaluated in this report were performed, had less optimal physical dose characteristics with a low output (0,1 Gy/min) and also less optimal beam profiles than modern megavoltage linear accelerators.

Four randomized studies have evaluated the efficacy of neutrons in comparison to photons [3,16,18,37].

The literature shows that:

- Neutron radiotherapy is not superiour to photon radiotherapy with regard to local control and survival in invasive bladder cancer.
- Neutron treatment entails unacceptably high number of serious late side-effects, with a high frequency of fatal outcomes.
- The increase in fatal side-effects, in some studies, has resulted in decreased survival in neutron-treated patients.

Neutrons.

	1 = High	2 = Moderate	3 = Low	Total
C	–	2/220	2/99	**4/319**
Total	**–**	**2/220**	**2/99**	**4/319**

Palliative radiotherapy – hypofractionation
Overview 3 (after the list of references)

The optimal method of palliative radiotherapy in invasive bladder cancer causing local symptoms is a matter of discussion. Many patients with bladder cancer are too old and fragile for curative radiotherapy or have distant metastases and a short expected survival. The goal for palliative treatment is relief of symptoms.

In a recent large RCT, hypofractionated and conventionally fractionated RT were compared with regard to the relief of symptoms [13].

The literature shows that:

- Radiotherapy rapidly and effectively decreases tumour-induced bladder symptoms.
- Short time (one week), hypofractionated palliative radiotherapy gives similar symptom improvement as a two week daily treatment.

Palliative radiotherapy.

	1 = High	2 = Moderate	3 = Low	Total
C	1/500		–	**1/500**
Total	**1/500**	**–**	**–**	**1/500**

Radiotherapy response modifiers

Overview 4 (after the list of references)

Hyperbaric oxygen

The use of hyperbaric oxygen is based on the hypothesis that the radiosensitivity of tumour cells varies with the degree of oxygenation and on the belief that some tumours contain foci of anoxic cells. Thus hyperbaric oxygen might be of benefit in connection with radiation treatment, since hypoxic cells are more radioresistant than fully oxygenated cells. Three randomized studies have evaluated the effects of hyperbaric oxygene [9,12,36].

Hyperthermia

Increased temperature (40–45°C) damages cells, especially cells in hypoxic, nutrient-deprived and low pH environments, as is often the case in tumours. The combination of hyperthermia and radiotherapy has been suggested to act synergistically and clinical benefit has been reported in treatment of different tumours.

One RCT evaluated the efficacy of radiotherapy in hyperthermia [48].

Misonidazole

During the 1970s it was shown in experimental studies that misonidazole could sensitize hypoxic tumour cells to irradiation and that this drug also accumulated in tumour tissue. It was therefore tested in clinical studies.

Three small RCT were performed in patients with bladder cancer [1,8,35].

The literature shows that:

- The use of hyperbaric oxygen does not improve the efficacy of radiotherapy in muscle invasive bladder cancer.
- The addition of hyperthermia to radiotherapy increases the complete response rate, but does not prolong the duration of local control.
- The use of misonidazole to sensitize hypoxic tumour cells prior to radiotherapy does not increase downstaging, or improve survival or local control in patients with muscle invasive urinary bladder cancer.
- Misonidazole entails substantial toxicity, especially severe neuropathy.

	1 = High	**2 = Moderate**	**3 = Low**	**Total**
RCT	1/236		6/457	**7/693**
Total	**1/236**	**–**	**6/457**	**7/693**

Cystectomy with or without preoperative radiotherapy

Overview 5 (after the list of references)

The aims with the use of RT prior to cystectomy are to eradicate microscopic extravesical disease and to prevent seeding of tumour cells at surgery. The value of preoperative radiotherapy has been evaluated in four randomized trials [2,5,43,44]. The only large study with 471 patients is hampered by the fact that approximately 50 per cent of the randomized patients did not complete the planned therapy [43].

The literature shows that:

- The evaluation of preoperative radiotherapy still lacks well designed large randomized studies.

Cystectomy vs. pre-op radiotherapy + cystectomy.

	1 = High	2 = Moderate	3 = Low	Total*
M	–	–	1/(402)	**1**
C	–	1/124	3/350	**4/474**
Total	**–**	**1/124**	**4/350**	**5/474**

*) In the figures within brackets all patients reported in the individual articles are counted. Many patients are reported in more than one article and the figures without brackets indicate number of patients only counted once.

Preoperative radiotherapy + cystectomy versus radiotherapy

Overview 6 (after the list of references)

The efficacy of radiation treatment as monotherapy in bladder cancer has been investigated in several trials. But, no randomized trials comparing surgery alone with radiotherapy alone have been performed. Three studies evaluated preoperative radiotherapy followed by cystectomy versus radiotherapy alone with salvage cystectomy [7,30,41]. Side-effects in the Sell study [41] have been reported separately [31], and a 10-year update [25] has been performed of the Bloom study [7]. Each study has insufficient power to establish definitive treatment recommendations and only the smallest study showed an overall survival benefit for the patients treated with primary cystectomy. A Cochrane meta-analysis [42] has been performed including the randomized studies performed 1966–86 [7,25,30,41]. The conclusion was: "the evidence consistently favour surgery" (with preoperative radiotherapy) but "the randomized trials evaluated in this analysis were not recent and major advances have been made since these trial commenced in both surgery and radiotherapy".

Patients with pT0 after preoperative radiotherapy, have the most favourable outcome, suggesting that this could be used as a predictive factor in bladder preserving strategies.

The literature shows that:

- The studies performed between 1966–86 consistently favour preoperative radiotherapy followed by cystectomy versus radiotherapy with salvage cystectomy regarding survival, but causes more morbidity. The Cochrane overview showed survival benefit for preoperative radiotherapy and cystectomy. A sufficiently powered randomized study is needed to provide convincing evidence.
- The tumour response rate after preoperative radiotherapy (40–50 Gy) is a good prognostic/predictive factor for survival.

Preoperative radiotherapy + Cystectomy vs. radiotherapy + Salvage Cystectomy.

	1 = High	**2 = Moderate**	**3 = Low**	**Total**
M	1/(439)	–	–	**1/(439)**
RCT	–	2/372	1/67	**3/439**
R	–	–	–	**–**
O	–	–	–	**–**
Total	**1**	**2/372**	**1/67**	**4/439**

Radiotherapy – side effects

Overview 7 (after the list of references)

One trial has compared toxicity after a standard radiotherapy plan with a 3D conformal plan [46].

The antioxidant agent Cu/Zn superoxide dismutase (SOD), which functions as a free radical scavenger, has been tested for reducing acute and late radiation side effects in two randomized trials [33,40].

The literature shows that:

- The influence on toxicity of the amount of normal tissue within the treatment volume is still unclear.
- Medication with SOD was reported to diminish radiotherapy induced side-effects. A possible tumour protective effect has not been evaluated.

Side-effects.

	1 = High	2 = Moderate	3 = Low	Total
RCT	–	1/442	2/119	**3/561**
Total	**–**	**1/442**	**2/119**	**3/561**

Miscellanous treatment (chemoradiotherapy, immunomodulation)

Overview 8 (after the list of references)

Only one randomized study comparing chemoradiotherapy with radiotherapy alone was found [10].

In SBU 155/1 [34] the following was stated concerning chemotherapy combined with either surgery or radiotherapy: "Bladder preservation can be achieved in selected patients by using combination chemotherapy and surgical resection or radiotherapy. Although results from phase II studies show survival data similar to those in cystectomy patients, no controlled studies have yet been performed on bladder sparing treatment vs. cystectomy. Chemotherapy can be safely administered concomitantly with curative radiotherapy and induces tumour responses in the majority of cases. However, no controlled studies have yet been performed on chemoradiotherapy vs. radiotherapy alone or radiotherapy preceded by neoadjuvant chemotherapy."

Bestatin, a metabolite of Streptomyces olivoreticuli, has immunopotentiating properties and inhibits growth of tumours in experimental models. It has been investigated in one randomized trial [6]. No benefit was found.

Literature

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).*

	1 = High	2 = Moderate	3 = Low	Total
M	1/(439)	1/(345)	1/(402)	**3**
C	2/736	10/1 845	21/1 752	**33/4 333**
Total	**3/736**	**11/1 845**	**22/1 752**	**36/4 333**

*) In the figures within brackets all patients reported in the individual articles are counted. Many patients are reported in more than one article and the figures without brackets indicate number of patients only counted once.

Conclusions and comments

Radiotherapy for muscle invasive non-metastatic bladder cancer was considered standard therapy in some countries in the 70s and 80s. Without strong scientific evidence, standard therapy in these countries changed from radiotherapy for invasive bladder cancer to cystectomy. The reason for this was probably the rapid development of improved anuesthesia and surgical techniques during the 80s and 90s including new techniques for urinary diversion. The non-significant trends in the early randomized studies favouring pre-operative radiotherapy combined with cystectomy could have influenced the choice of surgical treatment for healthier and younger patients. Radiotherapy was reserved for older and less medically fit patients. Many papers have been published on phase II studies showing a tendency for improved outcome with surgical treatment (not reviewed in this report), but this might be due to a selection bias. So, radiotherapy as a primary therapy for bladder cancer was abandoned without any clear scientific evidence.

The evaluation of radiotherapy in invasive bladder cancer is hampered by the fact that most studies are small, have low power and sometimes more than one question is asked in the same study. Only occasional studies have included more than 200 patients. In many of the more recent studies the follow-up time is still short.

- There is moderate evidence for an overall survival benefit with pre-operative radiotherapy followed by cystectomy compared to curative

radiotherapy based on early studies (1964–1986). Since that time surgical as well as radiation techniques have developed considerably. Therefore, the conclusion may not be relevant to modern treatment of invasive urinary bladder carcinoma. ([42]M1, [7]C2, [25]C2, [41]C2, [30]C3).

- There is only one small study reporting on curative radiotherapy where increased dose per fraction is compared to conventionally fractionated radiotherapy to the same total dose. Thus, no conclusions can be drawn concerning optimal fraction dose. ([19]C3).
- A meta-analysis based on two studies on hyperfractionated radiotherapy gives moderate evidence of a survival benefit at five and ten years and an increased local control rate compared to conventional fractionation. ([45]M2, [23]C2, [32]C2).
- The documentation of local control and overall survival rate after split-course radiation treatment compared to continuous therapy is conflicting. No firm conclusions can be drawn. ([24]C3, [27]C3, [29]C2).
- Four small and early studies have compared radiation treatment using neutrons with photon treatment. The reports favour therapy with photons with respect to overall treatment results. There is a moderate evidence for this conclusion. ([3]C3, [14]C2, [18]C3, [37]C2).
- There is fairly strong evidence in early studies that radiation treatment in combination with hyperbaric oxygen does not confer a treatment benefit compared to radiation in normal atmosphere. ([9]C1, [12]C3, [36]C3).
- There is no indication of a treatment benefit with the addition of either hyperthermia or misonidazole to radiation treatment in invasive bladder carcinoma. ([48]C3, [1]C3, [8]C3, [35]C3).
- A large number of phase II studies, suggesting an increased possibility for bladder preservation with concomitant chemoradiotherapy compared to radiotherapy alone, has been reviewed in a previous SBU report on chemotherapy, 155 [34]. Only one small randomized study

has been reported where concomitant chemoradiotherapy with cisplatin is compared to radiation alone. No conclusion on the therapeutic benefit of combined treatment can be drawn. Large randomized studies are needed. ([10]C3).

- There is some evidence that preoperative radiotherapy followed by cystectomy does not confer any significant survival benefit compared to cystectomy alone. ([26]M3, [2]C3, [5]C3, [43]C3, [44]C3).
- There is moderate evidence that palliative radiotherapy of invasive bladder carcinoma can rapidly induce tumour related symptom relief. ([13]C1).
- There is moderate evidence that palliative hypofractionated radiotherapy, 3 fractions during one week, gives the same relief of symptoms as 10 fractions during two weeks. ([13]C1).

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Overview 1 *Urothelial bladder cancer. Radiotherapy as definitive treatment – radiation dose, fractionation, schedule.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Finney 1971 [19] C	Influence of RT dose: survival, side effects **A:** 2.0 Gy/fr, 65 Gy/6.5 w **B:** 2.5 Gy/fr, 65 Gy/5 w **C:** 3.0 Gy/fr, 65 Gy/4w 4 MeV, 3 fields, 8 x 8 – 10 x 10 cm	1959–1962 T1 T2 T3 A 36 pts 8 28 – B 36 pts 11 25 – C 37 pts 10 24 3 Included 109 out of total 385 pts treated for bladder cancer during the period Follow-up >5y
Quilty 1985 [39] C	Influence of RT dose: survival, side effects Tumour ≤5cm **A:** 2.5 Gy/fr, 50 Gy/4 w **B:** 2.88 Gy/fr, 57.5 Gy/4w Tumour >5–8 cm C: Same RT as A D: 2.63 Gy/fr, 52.5 Gy/4 w	1973–1975 A 29 pts B 26 pts T1 (24%), T2 (58%) T3 (16%), T4 (2%) C 17 pts D 22 pts T1 (25%), T2 (28%) T3 (44%), T4 (3%) Follow-up ≥8 y
Finney 1980 [20] C	Influence of RT dose: survival, local control, side effects **A:** 3.0 Gy/fr, 57 Gy/24 d **B:** 4.6 Gy/fr, 45.8 Gy/11d	T1 T2 T3 A 37 pts 1 30 6 B 37 pts 1 26 10 Follow-up > 5y

CI: confidence interval; HF: hyperfractionated; HFRT: hyperfractionated radiotherapy; LCR: local complete remission; MST: median survival time; ns: no significant; NED: Alive No Evidence of Disease; OS: overall survival; pts: patient(s); RCT: radiochemotherapy; RT: radiotherapy; w: week(s); m: month(s); y: year(s)

Results				Conclusion/Comments
	OS% at 5 y	**OS% G.1**	**OS% Anaplastic**	Few patients and 3 groups gives low power in the study.
A	25	18	14	A trend for increased OS was seen with 3.0 Gy.
B	19	22	15	No difference in bladder reactions
C	41	42	15	Rectal reactions increased in incidence and severity with increased fraction dose.
p=0.07				**C3**
Late side-effects:				
1 major bladder contracture, 4 major rectal complications				
Pts alive/salvage cystectomy performed: A 3/7, B 0/4, C 3/4. 13/15 pts operated <18 m after RT.				

	OS%			**Late toxicity gr. 3–4 %.**		Complex study with few patients in each group.
	5y	**8y**		**Bladder**	**Bowel**	**C3**
A	55	48	A+C	13	5	
B	58	46	B	28	9	
C	29	23				
D	41	33	D	44	6	

	OS%	**LCR% at 5 y**	**% pts with urin sympt**		Survival superior in A with higher total dose, especially in T2 tumours (37% vs. 12%).
			Frequency	**Dysuria**	B: 1 pts required a colostomy, and in 40% of cases severe rectal reactions
A	32	37	38	27	**C3**
B	11	11	24	27	

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Stuschke 1997 [45] M	Benefit of hyperfractionated RT meta-analysis of HRT. Data from ref [17,23].	Ref [17]; 168 pts, (same pts as in ref [32]) Ref [23]: 177 pts
Näslund 1994 [32] C Edsmyr 1985 [17] C	Benefit of hyperfractionated RT **A:** 2.0 Gy/fr, 1 fr/d, 64 Gy/8 w **B:** 1.0 Gy/fr, 3 fr/d, 84 Gy/8 w, 2 w split. 4 h between fractions Regional lymph nodes within 75% and bladder within 100% isodose curve	1971–1978 T2 (33%), T3 (45%), T4 (22%), G3 (96%) A 85 pts B 83 pts Mean age 68 y Follow-up >10 y No pts excluded
Goldobenko 1991 [23] C	Benefit of hyperfractionated RT **A:** 2.0 Gy/fr, 60.0 Gy/8 w **B:** 1.0 Gy/fr, 2 fr/d, 60.0 Gy/8 w **C:** 1.0 Gy/fr, 2fr/d, 70.0 Gy/9 w **D:** 1.2 Gy/fr, 2 fr/d, 67.5 Gy/7.5 w 2 w split in all groups	1980-1987 T2–T3 A 43 B 26 C 61 D 47
Cox 1988 [11] RTOG 8308 C, phase I–II	Hyperfractionated RT: side effects **A:** 1.2 Gy/fr, 2 fr/d, 60.0 Gy/5 w **B:** 1.2 Gy/fr, 2 fr/d, 64.8 Gy/5.5 w **C:** 1.2 Gy/fr, 2 fr/d, 69.6 Gy/6 w RTOG protocol (83–08) 4–8 h between fractions	1983–1986 T2 N+; T3–4 (80%); A 9 B 15 C 26 Follow-up minimum 18 m

Results	Conclusion/Comments
Odds ratio for death in HRT groups **(95% CI) p value** Ref [17] 0.61 (0.38–0.96) 0.03 Ref [23] 0.43 (0.21–0.86) 0.02 Pooled data 0.55 (0.37–0.8) 0.002 T3 tumours 0.39 (0.23–0.67) 0.001 **Odds ratio for LCR** Pooled data 0.44 (0.27–0.72) 0.001	Survival data collected from published curves. Improved survival was seen with hyperfractionation. Higher odds ratio for death in T3 than T2. **M2**
OS% 5 y 10 y LCR% A 22 0 36 B 34 10 65 p =0.01 p=0.003 p=0.01 Major complications: A 5%, B 12% Colostomy A 4 pts B 7 pts	Report on long-term results of pts treated 1971–78 ref [17] and followed 10 y. Well performed study. Survival benefit in HRT group. **C2**
OS% LCR% at 3y A 44 16 B 52 23 C 69 34 D 66 23	Odds ratio for deaths in HRT groups sign lower than conventional RT (p=0.02) reported in ref [45]. **C2**
Late toxicity (gr 3–4) % (actuarial) 6 m 12 m 18 m 24 m A+B+C 5 7 10 10 C 5 5 11 11	Very small study. No control group. No obvious deleterious increase in side effects in comparison to RTOG 7104 ref [29]. **C3**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Marcial 1985 [29] RTOG 7104 C	Split-course: survival, local control, side effects **A:** 2.0 Gy/fr, 60 Gy/6 w **B:** 2.75 Gy/fr, 10 fr, 2–3 w split, 2.75 Gy/fr, 10 fr, total dose 55 Gy/6–7 w	1971–1980 139/148 pts evaluable A: 73 B: 75 Stage C (58%), N+ (40%) 66% >5 cm diam. Median age 69 y (45–80) y 22% died during therapy. Follow-up >5 y
Kob 1985 [27] C	Split-course: survival, local control, side effects **A:** 1.5 Gy/fr, 60Gy/8 w **B:** 3 Gy/fr, 10 fr, 4 w split, 3 Gy/fr, 10 fr, total dose 60 Gy/8w, 4 fields	1980–1984 T1 (25%), T2 (41%), T3 (27%), T4 (7%) A 95 pts B 95 pts Age: 60–79 y
Holsti 1969 [24] C	Split-course: survival, local control, side effects **A:** 2.0 Gy/fr, 6 fr/w, 60 Gy **B:** Same as A but 5–10% increase in total dose and 2 w split, treatment time 8 w	1963–65 33 pts not randomized Rand pts / Not rand pts / Total A 25 / 20 / 45 B 15 / 13 / 28

Results						Conclusion/Comments
	MST, m	**OS%**		**LCR%**		Bladder cancer was a subgroup within RTOG 7104
		3 y	**5 y**	**3 y**	**5 y**	
A	11.5	18	12	76	51	No diff. in survival or tumour control.
B	9.4	21	15	57	57	No diff in side effects.
LCR tumour <5 cm 61 %, 5–7.9 cm 33%, >8 cm 24%						No CT staging. Low RT doses.
Toxicity severe acute:			A 57%	B 49%		**C2**
moderate late:			A 9%	B 4%		
severe late:			A 2%	B 10%		
	OS% 5 y	**LCR% at 6 m**				Short follow-up.
A	52	90				Trend for improved survival in A,
B	39	90				but more advanced tumours in B.
	p=0.03					No difference in local control
						C3
	OS%	**LCR%, at 2 y**				Small study, short follow-up 33 non-randomized patients added to the
A	29	21				randomized population.
B	36	24				**C3**

Overview 2 *Urothelial bladder cancer. Radiotherapy with photons versus radiotherapy with neutrons.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Duncan –1985,-86, [14,16] C	Survival, local control, side effects **A 1:** 2.75 Gy/fr, 55 Gy/4w. T1–3 **2:** 2.4 Gy/ fr, 47.5 Gy/4 w. T4 **B 1:** RT neu 0,825 Gy/fr, 16,5 Gy/4 w T1–3 **2:** RT neu 1.28 Gy/fr, 12,8 Gy/2 w T4 **A1:** 3 fields max. rectal dose 52,2 Gy **A2:** 4 fields (WP), max rectal dose 47.5 Gy **B1:** 6 fields max rectal dose 14.8 Gy **B2:** 4 fields (WP), max rectal dose 15.0 Gy	1978–1981 T1–T4, any N, M0 A 60 pts B 53 pts Age < 80 y Follow-up median 5 y (min 30 m)
Pointon 1985 [37] C	Survival, local control, side effects **A:** 3,44/fr to 52,5–55 Gy/21 d (rotation technique) **B:** RT neu 15 MeV, 6 fields 1: LDN, 16.5 Gy/21 d. 2: HDN, 18.5 Gy/21 d. **C:** A + B (Due to technical reasons, some pts received mixture of photons and neutrons)	1978–1981 107/108 pts eligible T2 –T3, TX. 80% T2b–3. A: 59 pts B1: 20 pts B2: 20 pts C: 8 pts Age <73 y. 16 did not complete treatment
Battermann 1982 [3] C	Survival, local control, side effects **A:** 2.5 Gy/fr, 50Gy/4 w **B:** RT neu 14MeV, 6 fields **1.** 0.85 Gy, 17 Gy/4 w **2.** 0.95 Gy, 19 Gy/4 w	1978–1981 T4b A: 6 pts B1: 12 pts B2: 12 pts
Errington 1991 [18] C3	Survival, side effects **A:** 2.0 Gy/fr, 44 Gy/4.5 w (WP) + boost 2.0 Gy/fr, 20 Gy/2 w, total dose 64 Gy/6.5 w **B:** RT neu 8 MV, 3–4 fields, isocentric 1.6 Gy/fr, 14.4 Gy/3 w (WP) + boost 1.6 Gy/fr, 4.8 Gy/1 w, total dose 19.2 Gy	1986–1990 Randomization 1:3, 1986–87 1:1, 1988–90 T3a–T4, Nx–2, M0 A 28 pts B 41 pts Age <80 y

fr: fraction(s); HDN: high dose neutrons; LCR: local complete remission; LDN: local dose neutrons; m: month(s); ns: not significant; pts: patient(s); RT: radiotherapy; RT neu: radiotherapy with neutrons; w: week(s); WP: whole pelvis

Results						Conclusion/Comments
	OS%	**LCR% at 5 y**				WP fields to T3 pts was used during initial 14 m of trial. Similar LCR but inferior OS due to treatment related deaths. **C2**
		All pts	**T1/2**	**T3**	**T4**	
A	45	43	77	35	30	
B	12	43	60	45	20	
	p=0.001					
Serious late morbidity: A 38% B 78% Treatment related death: A 2% B 16% Salvage cystectomy A 38%, but in B only 7% due to severity of pelvic fibrosis.						
	OS% 3y	**LCR%, 3–6 m**				No difference in survival or LCR. Increased late side effects with neutrons. **C2**
A:	42	69				
B:	46	70				
1:	55	69				
2:	40	75				
C:	38	–				
Major complications: A 5% B 19% Serious late effects: A 9% B 40% Fatal late effects: A 3% B 5% C 2 pts						
OS 1 y 40%, (estimated from survival curve) No difference between groups.						Small study, short follow-up. No difference in survival. More side effects with neutrons. **C3**
	OS% at 1 y					Low power, short follow-up. Bladder cancer pts was a cohort within a large neutron treatment study on different kinds of malignant tumours. **C3**
A	66					
B	39 ns					
Mortality: RR 0.66 (0.40–1.10) A vs B. No difference in early or late side effects						

Overview 3 *Urothelial bladder cancer. Palliative radiotherapy, hypofractionation.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Duchesne 2000, [13] C	Treatment efficacy **A:** 3.5 Gy/fr, 35 Gy/2 w **B:** 7.0 Gy/fr, 3 fr/w, 21 Gy/1 w Small field, only bladder.	1992–1997 (multicenter) T2 (18%), T3 (48%) T4a (13%) T4b (21%) Median age 79 y. Inclusion: local symptoms, >3 m expected survival, radical treatment not possible due to age, medical condition (T2–T4a) or advanced disease (T4b, N+, M1). 500 pts 321/500 assessed with QoL questionare (RSCL) Pre RT 313 pts 2 w post RT 268 pts 3 m post RT 167 pts

Results	Conclusion/Comments
Improvement in at least one bladder symptom, % **A** **B** End of RT 53 50 at 3 m 71 64 **Improvement of pretreatment symptoms at 3 m, %** **Symptom:** **n*** **A+B%** Urinary frequency 50 82 Nocturia 96 64 Hematuria 188 88 Dysuria 120 72 No difference between A and B n*= number of pts with symptoms pre RT and evaluated at 3 m. Duration of improvement median 9 m from start of RT. No difference in OS between groups. MST 7.5 m	No sign difference between groups in survival or palliative effect. Optional cystoscopy in 70 pts at 3 m. did not show any difference in LCR (A 55%; B 38%). **C1**

Overview 4 *Urothelial bladder cancer. Radiotherapy – response modifiers.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Cade 1978 [9] C MRC	Benefit of hyperbaric oxygen RT: 1.5–2.5 Gy/fr, 60 Gy/ 5–8 w (133 pts) 4–4.25 Gy/fr, 42.5–47.25 Gy/4–5 w (51 pts) 6 Gy/fr to 36 Gy/fr /18d (57 pts) **A:** Air . **B:** HO, 3 ATM, RT 15 min after full pressure	1964–1971 T2 (48%); T3 (52%), Nx, M0 236/241 pts evaluable A: 118 pts B: 118 pts Age <75 y Follow-up 5 y
Dische 1973 [12] C	Benefit of hyperbaric oxygen Trial 1: **A:** 2,0 Gy/fr, 60 Gy/42 d in Air **B:** same RT with HO, 3 ATM Trial 2: **C:** 3,15 Gy/fr, 3 fr/w, 47,25 Gy/ 33 d in Air **D:** same RT with HO, 3 ATM, RT 12–15 min after full pressure	1966–not reported Trial 1: 40 pts Trial 2: 27 pts A + C 33 pts B + D 34 pts
Plenk 1972 [36] C	Benefit of hyperbaric oxygen **A:** 2,5–3.0 Gy/fr, 60 Gy/42 d in Air **B:** 4,0 Gy/fr, 48 Gy/29–40 d in HO, 3 ATM, RT 8–10 min after full pressure Cobolt	1965–1970 T1–2 T3–4 A 21 pts 6 15 B 19 pts 5 14
van der Zee 2000 [48] C	Hyperthermia: survival, local control RT 2.0 Gy/fr, 66–70 Gy/7 w (WP 40 Gy) **A:** RT only **B:** RT + deep hyperthermia 42 °C, 60–90 min, 1/w, 5 times, 1–4 h after RT	1990–1996 T2– 4, N0, M0 mean RT dose A 56 pts 64.4 Gy B 58 pts 65.9 Gy Follow-up 3y

ATM: atmosphere; BED10: biological effective dose, a/b = 10; Bl. preserv: bladder preservation; d: day(s); fr: fraction(s); HO: hyperbaric oxygen; LCR: local complete remission; LPR: local partiell remission; m: month(s); NR: not reported; ns: not significant; OS: overall survival; RT: radiotherapy; w: week(s); y: yera(s)

Results	Conclusion/Comments
OS% **3 y** **5y** A 37 30 B 36 28 No difference in LCR or in morbidity	HO treatment did not improve survival. **C1**
OS% **3 y** **5y** A 37 25 B 27 20 Moderate/severe toxicity A: 0 pts, B: 3 pts.	No difference in survival. 6 pts. allocated to HO were treated and analysed as Air patients. **C3**
OS% **3 y** A 8 B 14 00.05 Morbidity not reported	Early results, small study, but a trend for improved survival was seen in B. Different fractionation and total dose in A and B **C3**
OS% **LCR%** **LCR%** **3y** **3 m** **3y** A 22 51 33 B 28 73 42 p=0.01 No difference in duration of LC. Late toxicity did not differ between groups (12%).	Significant increase in LCR at 3 m, but not in duration of response, LCR 3 y or OS. 1 patient in each group died of RT related late toxicity. **C3**

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Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Abratt 1991 [1] C	Benefit of addition of misonidazole (M) to RT: RT 2.0 Gy/fr, 20 fr, all pts **A:** 2.0 Gy/fr, 10 fr, + placebo, total RT dose 60 Gy/5 w **B:** 6.0 Gy/fr, 2 fr, + M, total RT dose 52 Gy/5 w	1981–1985 T2 17%,T3 83%; 53/58 pts evaluable A 26 pts B 27 pts Follow-up > 5y
Papavasiliou 1983 [35] C	Benefit of addition of misonidazole (M) to RT: RT 4.0 Gy/fr, 2 fr/w, 32 Gy/4 w + boost 4.0 Gy/fr, 2 fr/w, 16 Gy/2 w total dose 48 Gy/6 w **A:** RT + placebo **B:** RT + M	1979–1981 T3–4, Nx, M0 T2 T3 T4 A 47 pts 17 30 3 B 47 pts 17 26 7 Age <80 y Follow-up time not reported
Bydder 1989 [8] C	Benefit of addition of misonidazole (M) to RT: RT 2 Gy/fr, 20 fr, 40 Gy/26 d **A:** RT + placebo **B:** RT + M + in both groups: boost 2.0 Gy/fr 10 fr, 20 Gy/12 d, or cystectomy	1980–1983 T1 –T4 A: 43 pts B: 46 pts Age <75 y Follow-up >3 y

Ref [1]: misonidazole, 3g/ m^2/d per os + intravesically 1g 4 and 2 hour before RT
Ref [35]: misonidazole, 0.6 g/ m^2/day, maximum 1.2 g; Max. total dose 12 g/m^2
Ref [8]: misonidazole, 1g/ m^2/d per os to 12 g total dose

Results				Conclusion/Comments
	OS% 5y	**LCR% 6 m**	**LCR% 5y**	Small study. Different RT-schedules.
A	41	63	46	No effect of misonidazol on OS or LCR.
B	48	69	36	**C3**
More side-effects in B				

	LCR %	**Neuropathy %**	Unconventional fractionation. No effect of misonidazol.
A	66	2	
B	72	15	**C3**
No diff in RFS Side-effects, except neuropathy, were similar			

	LCR% at 3y	**Neuropathy**	No effect on LCR or downstaging. OS not reported per group. More T2 tumours in B (10 vs 19). More T3 tumours in A (24 vs 18). Misonidazole induced persistent and severe neuropathy. **C3**
A	32	7	
B	53	43	
	ns	p=0.001	
More pts in B did not complete RT.			

Overview 5 *Urothelial bladder cancer. Cystectomy with or without preoperative radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Huncharek 1998 [26] M	**A:** Cystectomy **B:** RT 2–5 Gy/fr, 20–54 Gy/1–4 w + cystectomy	5 trials, 4 with 5 y OS data 754 pts included (NSABP 47% of patients)
Smith Jr 1997 [44] SWOG C	**A:** Surgery **B:** RT 4.0 Gy/fr, 20 Gy/1 w, WP + surgery	1982–Not reported CIS 6%, T1 7% (rapidly recurring) T2 23%, T3 64%, M0 124/140 pts evaluable Reason for exclusion: histopathology 12 pts; No surgery 4 pts A 64 pts B 60 pts Follow-up 5 y
Anderstrom 1983 [2] C	**A:** Surgery **B:** RT 1.75–2.4 Gy/fr, 32–54 Gy/4–6 w + surgery. Op 2–4 w. post RT	1970–78 T2 G3¸T3a 44/51pts evaluable A 22 pts B 22 pts Follow-up not reported

BED: biological effective dose; CIS: cancer in situ; CSS: cause specific survival; fr: fraction(s); pLCR: pathologic local complete remission; m: month(s); nr: not reported: ns: not significant; OR: odds ratio; OS: overall survival; pts: patient(s); RT: radiotherapy; WP: whole pelvis; w: week(s); y: year(s)

Results	Conclusion/Comments
Odds ratio for death, (95% CI) B vs A 3 y 0.91 (0.64–1.30) 5 y 0.71 (0.48–1.06) Excluding ref [43] 5y 0.94 (0.57–1.55)	Data extracted from each published report. ([2,43,44]) OR at 3y and 5y does not show any benefit for pre-op RT **M3**
OS% 5 y **MST, y** A 53 5.3 (3,2–7,7) B 43 2.3 (1,3–5,6) Side-effects not reported	Long follow-up. No benefit from preop RT with this dose and schedule. Only chest x-ray as staging procedure, and no analysis according to T-stage. **C2**
OS% 3y **pLCR% 5y** A 81 61 18 B 81 75 55 p=0.027	Small study. Variation in RT dose and schedule. 10 pts got a total dose >40 Gy and these pts had a better outcome (OS, pT0). Good prognosis in pts who were tumour free (pT0) at op. **C3**

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Overview 5 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Slack 1977 [43] C	**A:** Surgery **B:** RT 1.8–2.2 Gy/fr, 45 Gy/28–32 d + surgery, within 30–60 d During the 1st half of the trial, 5-FU was given as adj. treatment in both groups.	1964–1970 T1 (37%), T2 (42%), T3 (17%) N+ (4%) 234/47l pts evaluable A 131 pts B 103 pts Follow-up >5 y
Blackard 1972 [5] C	**A:** Surgery (26 pts total cystectomy, 9 pts partial cystectomy,) **B:** RT 2 Gy/fr, 50–60 Gy/5–6 w **C:** RT 2 Gy/fr, 45/4–5 w + surgery	1965–1970 T2–3 T2 T3 A 22 pts 12 10 B 27 pts 10 17 C 23 pts 12 11 Mean age 65.5 y 18 pts did not complete their assigned treatment. Follow-up 2 y

Results	Conclusion/Comments
OS% 5y **pLCR%** **All T1 T2 T3+N+ T1 T2 T3+N+** A 33 44 31 22 19 3 4 B 45 69 42 19 40 32 32 p value nr In pts not given chemotherapy OS% at 5 y, was sign. improved in B (A: 25%, B: 52%)	Long follow-up. However, approximately 50% of patients did not complete prescribed therapy and were excluded. Despite a large number of remaining patients, this fact hampers the interpretation of the data. **C3**
OS% A 42 B 59 C 52 5 (14%) post op deaths	Small study. 340 of 412 pts admitted with bladder cancer were not included due to T1 or T4 stage, age, medical problems. Excluded from meta-analysis, ref [26] due to short follow-up **C3**

Overview 6 *Urothelial bladder cancer. Preoperative radiotherapy + cystectomy versus radiotherapy.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Shelly (Cochrane) 2002 [42] M	3 studies ref [7,30,41] **A:** RT + salvage cystectomy **B:** Preop RT+cystectomy Detailed technique see resp. ref.	ITT: 439 pts TR: 378 pts T2–T4a N0, M0 A 216 pts (11 pts not treated as assigned) B 221 pts (42 pts not treated as assigned)
Wallace 1976 [47] Bloom 1982 [7] Horwich 1999 [25] C	**A:** RT 2.0 Gy/fr, 40 Gy/4, WP + boost 2.0 Gy/fr, 20 Gy/2 w, total dose 60 Gy/6 w Boost=bladder + perivesical tissue **B:** RT 2.0 Gy/fr to 40 Gy/4, WP + surgery within 4–8 w The outcome of the trial has been reported at 3 different times. By Wallace 1976 as OS, by Bloom 1982, and Horwich 1999 as OS and DSS.	1966–1975 T3 , M0 189/199 pts evaluable A 98 pts B 91 pts Age <71y 23% of pts in A, 7% in B did not complete planned treatment. Follow-up: All > 5y; 90% >7y; 40% >10 y

*ITT: analysis based on "intention to treat"; **TR: analysis based on pts who received planned treatment;
DSS:disease specific survival; fr: fraction(s); ns: not significant; OS: overall survival; pts: patient(s); RT: radiotherapy;
WP: whole pelvis; w: week(s); m: month(s); y: year(s)

Results	Conclusion/Comments
ITT-analysis (>1 = favours cystectomy) OS 3y 1.91 (1.30–2.20) ref [7,30,41] OS 5y 1.85 (1.22–2.82) ref [7,30,41] DSS 3y 1.65 (0.92–2.95) ref [7] DSS 5y 1.38 (0.75–2.54) ref [7] DSS 10y 1.77 (0.92–3.40) ref [25] **TR-analysis** OS 3y 1.84 (1.17–2.90) ref [41,47] OS 5y 2.17 (1.39–3.38) ref [30,41,47] DSS 3y 1.96 (1.06, 3.65) ref [7] DSS 5y 1.78 (0.94, 3.37) ref [7]	"the evidence consistently favour surgery" but "analysis were not recent and major advances have been made since these trial commenced in both surgery and RT…" "propose a further randomized trial of sufficient power.." No study with cystectomy vs. RT. Low dose RT in group A. **M1**
DSS% (ITT*) **pts<60 y** **DSS% (TR**)** **3 y** **5y** **10 y** **3 y** **5y** **10 y** A 33 29 20 25 36 31 B 45 38 30 49 53 44 A: salvage cystectomy 21%. OS at 5 y 60% B: pT0 after RT in 49% of pts. OS at 3 y 55% if pT0 vs 22% if not pT0 Surgical mortality A 11% B 7.8% Wallace: 60% of pts followed >5 y: OS 3y A 28% vs B 41% (p=0.06) 5y A 21% vs B 33% (p= 0.08)	Low RT dose in A. No. diff. in OS, but preop Rt + surgery improved outcome in younger patients (<60 y.) No evaluation of side effects. **C2**

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Overview 6 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Sell DAVECA 1991 [41] C	**A:** RT 2.0 Gy/fr, 40 Gy/4 w to WP, 2 w split, boost 2.0 Gy/fr, 20 Gy/2 w, total dose 60 Gy/8 w Boost=bladder + perivesical tissue **B:** RT same as A to 40 Gy/4w + surgery within 4–6 w	1983–1986 183 pts Stage% T2 T3 T4a A 95 pts 37 53 10 B 88 pts 42 49 9 N+ = 30% Age <71y Zelen randomization A: 7 pts did not follow the treatment plan B: 22 pts did not follow the treatment plan (11 of these pts refused surgery) follow-up median 50 m
Mommsen DAVECA 1989 [31] C	Analysis of side effects in pts included in ref [41].	Mailed questionnaire At 6 m 107 pts, 74% responded to questionaire. At 12–18 m 68 pts, 62% responded to questionaire.
Miller 1977 [30] C	**A:** RT 2.0 Gy/fr, 50 Gy/5 w to WP + boost 20 Gy/2 w. **B:** RT same as A to WP + cystectomy with node dissection	1964–70 Large T3 , M0 67/68 evluable A: 32 B: 35 Follow-up >5 y

Results	Conclusion/Comments
OS%. **3 y** **5 y** **MST, m** A: 33 29 18 B: 45 38 20 A B **Local recurr, %** **Dist metastases, %** A 36 32 B 7 34 p=0.05 Salvage cystectomy: A 28%. A: 12.5% major bladder and 17% moderate/severe rectal complications B: 9% moderate/severe rectal complications. Impotence (18 m): A 54%, B 100%.	Low RT dose in A No sign. diff in OS. Pts with salvage cystectomy had same 5 y OS as B pts. **C2**
Preop RT + cystectomy group (B) reported the largest reduction in social and sexual activites (100% impotent due to erectile dysfunction), and had more home care. At 6 m the RT only group (A) expressed a slightly more pessimistic outlook, but no difference at 12–18 m.	**C2**
ITT OS %, at 5 y A 16 B 46 p=0.01 A: 2 pts underwent salvage cystectomy. Both were alive > 5y, but registred as dead and counted as dead. If counted as alive OS% for group A=22%. In that case no difference in OS between A and B.	This report is included in an institutional overview from MD Andersson Hospital of pts with bladder cancer treated 1954–70 (724 pts). Small study. Difficult and unclear report. No side effects reported. **C3**

Overview 7 *Urothelial bladder cancer. Radiotherapy – side effects.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Tait 1993 [46] C	Analysis of acute RT side-effects in conventionally planned (CV) RT vs conformally planned (CF) RT. Different RT dose and schedule were used. 2.0 Gy/fr, 64 Gy/6.5 w (most pts) 6.0 Gy/fr, 1 fr/w, 30–36 Gy (for pts with poor general health) 1.8–2.0 Gy/fr, 2 fr/d, 58–64 Gy/4 w. (some pts) Each pts was planned both CV and CF and then randomized to be treated according to **A:** conventional RT plan **B:** conformal RT plan	1988–1993 90 pts Self assessment questionaire before RT, weekly during and 1 month after RT, monthly for 3 m
Sanchiz 1996 [40] C	Preventive drug RT 2.0 Gy/fr to 60 Gy/6 w to all + **A:** Placebo **B:** SOD, 8 mg, im. 15 min. after RT	1990–1995 432/448 pts evaluable T2 41%; T3 50%; T4 9% A 213 pts B 219 pts No difference in surgical procedures prior to RT
Nielsen 1987 [33] C	Preventive drug RT 2.1 Gy/fr, 63 Gy/6 w (3 fields, WP, rectal shield) to all + **A:** Placebo **B1:** SOD 4 mg **B2:** SOD 8mg	1979–not reported T1 47%; T2 23%; T3 20%, T4 10% (UICC 78) 30 pts A: 11 pts B1: 10 pts B2: 8 pts Follow-up 5 y

DFS: disease free survival; LCR: local complete remission; m: month(s); ns: no significant; OS: overall survival; pts: patient(s); RT: radiotherapy; SOD: Cu/zn superoxide dismutase: w: week(s); y: year(s)

Results	Conclusion/Comments
Normal tissue sparing approximately 40–50% using CF planning compared with CV. Analysis of acute side effects not completed. No correlation between rectal volume within 90% isodose curve and acute rectal toxicity was found.	Preliminary report. Analysis not finished. Authors conclusion "the assessment of the impact of volume on the level of acute symptoms in pelvic radiotherapy is complex, and requires analysis of a range of symptoms, dose levels and normal-tissue volumes". **C3**
	Acute toxicity% (gr 3–4)		Late toxicity% gr 1		gr 2	
	bladder	rectal	bladder	rectal	bladder	rectal
A	53	26	52	22	5	1
B	23	7	24	7	2	0
	p=0.0001	0.001	0.003	0.001		| No report on local control or survival	Large study, showing good protective effect of SOD on side effects. 2 pts excluded due to allergic toxicity. follow-up time NR. Same number of patients analysed for acute and late side-effects. Tumour protective effect by SOD not evaluated. **C2**
	OS%	**DFS%**	**LCR %, at 5 y**
A:	27	27	27
B1:	29	15	21
B2:	17	25	33	 No difference in acute side effects	Very small study. No tumour protective effect by SOD was demonstrated. 5 pts excluded due to allergic toxicity at the inj place. **C3**

Overview 8 *Urothelial bladder cancer. Miscellanous treatment (chemoradiotherapy, immunomodulation).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Coppin 1996 [10] C	Chemoradiotherapy RT 2.0 Gy/fr, 40 Gy/4 w, WP to all pts + 1. Cystectomy or 2. RT boost 2.0 Gy/fr, 20 Gy/2 w, total dose 60 Gy/6 w **A:** RT + 1 or 2 **B:** CHT co + RT + 1 or 2	1985–1989 T2/T3a 36%;T3b–T4a 53%; T4b 11% 99/102 pts evaluable 11 centers RT+1 RT+2 A 48 pts 23 25 B 55 pts 24 27 Age <76 y Follow-up median 6.5 y (min. 4 y)
Blomgren 1990 [6] C	Immunotherapy RT 2.0 Gy/fr, 64 Gy/8 w, 2 w split, (3 fields, WP, rectal shield) + **A:** Placebo **B:** Bestatin adj, 10 mg x 3 po, during 1y	1979–87 194/215 pts evaluable A 97 pts B 97 pts 19 pts did not complete RT. 2 pts excluded for other reasons. Follow-up 1.5–9.4 y

CHT: chemotherapy; fr: fraction(s); LCR: local complete remission; PPFS: pelvic progression-free survival; m: month(s); ns: not significant; pts: patient(s); RT: radiotherapy; w: week(s); WP: whole pelvis; y: year(s)
CHT co ref [10]: Cisplatin 100mg/m^2 every 2nd w x 3 during RT.

Results	Conclusion/Comments
OS% PPFS% **3 y 2 y 5 y** A 33 47 41 B 47 67 60 Pelvic recurrence: A 52%, B 29% Distant failure not different between groups.	Small study. Pelvic relapse rate was reduced in B, but no difference in survival. 78% received 3 cycles CHT. **C3**
No difference in overall survival, in all patients or in any subgroups.	No effect of Bestatin. **C2**