

Guidelines on **Bladder Cancer**

Muscle-invasive and Metastatic

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1. INTRODUCTION

One-third of patients with transitional cell carcinoma (TCC) of the urinary bladder will be diagnosed as having muscle-invasive or metastatic tumour. In addition, approximately 30% of patients who are initially diagnosed with a superficial TCC will develop an invasive tumour during follow-up after organ-preserving therapy.

The European Association of Urology (EAU) working group on muscle invasive and metastatic bladder cancer have provided the following recommendations based on scientific evidence for incorporation into the clinical practice of urologists and others involved in the management of patients with bladder cancer.

2. CLASSIFICATION

2.1 TNM staging

The Tumour, Node, Metastases (TNM) 2002 classification approved by the Union International Contre le Cancer (UICC, International Union Against Cancer) is widely accepted (1).

Table 1: 2002 TNM classification of urinary bladder cancer (1)

T (Primary tumour)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> ('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 tissue:
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall

N (Lymph nodes)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis 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	Metastasis in a lymph node more than 5 cm in greatest dimension

M (Distant metastasis)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

2.2 Histological grading

In addition, the histological classification of the World Health Organization (WHO) is generally applied throughout most of the world (Table 2).

Table 2: Histological grading of WHO and International Pathology Consensus Committee 1988 (2)

PTNM pathological classification	The pT, pN, and pM categories correspond to the T, N, and M categories of the TNM classification
G	Histopathological grading
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

More than 90% of bladder cancers are found to be TCC. The remainder are squamous cell carcinoma (SCC) or adenocarcinoma (3). Bladder tumours are considered superficial (Tis, Ta, T1) or infiltrative (T2, T3, T4) based on cystoscopy, transurethral resection (TUR), imaging studies and histopathological findings.

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3. RISK FACTORS

The risk factors for the development of bladder cancer are described in detail in the guidelines on superficial bladder cancer. In addition, it has to be stressed that chronic infection, residual urine and foreign bodies (for example indwelling catheters) are associated with invasive bladder cancer. However, these tumours are mainly squamous cell or adenocarcinomas. Similarly, tumours in bilharziosis are mostly invasive and only about one third are transitional cell carcinomas. In case tumours arise in persisting urachal remnants and true bladder diverticula, these tumours are invasive because of the intramural extension or thin bladder wall.

4. DIAGNOSIS

4.1 Symptoms

Painless haematuria is a common finding. In addition, there is a group of patients who complain of urgency, dysuria, increased frequency and pelvic pain. Pelvic pain and all the symptoms related to urinary tract obstruction are found in more advanced tumours.

4.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours.

4.3 Cystoscopy and TUR

The diagnosis of bladder cancer depends on cystoscopy, TUR and pathological evaluation of the resected lesion. Cystoscopy can provide good information on the extent of the tumour. The TUR specimen has to include the muscularis propria, which is achieved by separate TUR of the tumour base. A resection biopsy of the prostatic urethra should be done in male patients, while a bladder neck biopsy should be done in females in case the urethra is not resected totally or an orthotopic bladder substitution is considered. In addition, bimanual examination should be carried out before and after TUR to assess whether there is a palpable mass or the tumour is fixed to the pelvic wall (1,2).

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5. STAGING

5.1 T-staging

5.1.1 TUR and bimanual palpation

During TUR, tumour extent can be assessed by visualization of the deep muscle or perivesical fatty tissue. Biopsy of the prostatic urethra in men and of the bladder neck in women must be performed. In addition, bimanual examination before and after TUR should be performed to assess whether there is a palpable mass or the tumour is fixed to the pelvic wall (1,2).

5.1.2 Imaging

The aim of imaging is to assess the extent of the local tumour and to detect tumour spread to lymph nodes and other organs. Anatomical and functional information to help in making therapeutic decisions can be obtained using different imaging methods. If a local tumour is suspected to be invasive, patients should undergo imaging studies to assess the extent of invasion prior to undergoing TUR.

5.1.2.1 Intravenous pyelography

Intravenous pyelography (IVP) is the most commonly performed investigation. The detection of hydronephrosis indicates a poor prognosis (3).

5.1.2.2 Ultrasonography

Ultrasonography can be used as screening method to detect upper urinary tract obstruction. It may be used also for detection of metastases.

5.1.2.3 Computed tomography (CT)

Computed tomography (CT) cannot differentiate accurately between organ-confined and extravesical extension (4,5). The correlation between CT findings and tumour extent in cystectomy specimens is 65-80%. The imaging modality is helpful for monitoring patients undergoing neo-adjuvant chemotherapy or bladder-sparing treatment modalities.

5.1.2.4 Magnetic resonance imaging (MRI)

Similarly to CT, magnetic resonance imaging (MRI) cannot detect microscopic extension into the perivesical fat. The staging error remains about 30% (6,7).

5.2 N-staging

Both CT and MRI will miss microscopic nodal disease in a similar percentage of up to 70% (5,8,9).

It is suggested that three-dimensional (3D) MRI is more sensitive, but experience with this modality is limited (6). Positron emission tomography (PET) and laparoscopic lymphadenectomy in patients scheduled for bladder-sparing methods have not been fully investigated in prospective studies (10,11).

Lymphadenectomy is the only method capable of excluding metastatic disease to the lymph nodes.

The recommended extent of lymphadenectomy has not been assessed in prospective investigations.

5.3 M-staging

Prior to any treatment aimed at cure, it is essential to evaluate the presence of distant tumour. This includes the use of chest radiographs in all patients.

In addition, a pre-therapeutic bone scan should be performed in any patient who has symptoms that suggest bone involvement. Suspicious findings seen on bone scan should be confirmed by MRI (12). Otherwise, the use of a bone scan is an optional investigation. It should be noted that the serum level of alkaline phosphatase is not a reliable indicator for the presence of bone metastases (13).

Ultrasonography can be used as an inexpensive tool to demonstrate liver metastases. The sensitivity of abdominal CT has not been evaluated sufficiently to recommend this investigation routinely prior to curative therapy.

5.4 GUIDELINES ON DIAGNOSIS AND STAGING

Mandatory evaluations

- Physical examination
- Cystoscopy
- TUR
 - Biopsy of the tumour base
 - Biopsy of the prostatic urethra/bladder neck
- Chest X-ray
- IVP or abdominal sonography

Optional evaluations

- Abdominal CT/MRI
- Sonography of liver
- Bone scan

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6. PATHOLOGY

6.1 Urologist handling of the specimens

In TUR specimens, the superficial and deep areas of the tumour must be sent to pathology separately. If random biopsies of the flat mucosa have been done, each biopsy of the flat mucosa must also be sent separately.

In radical cystectomy, bladder fixation must be performed as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen in formalin; in some circumstances, this procedure can also be performed by the urologist.

6.2 Pathologist handling of the specimens

Handling of specimens should follow the general rules as published by a collaborative group of pathologists and urologists (1).

It must be stressed that it can be very difficult to certify the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, and it is therefore necessary to include the entire retracted or ulcerated area.

Amongst the margins, it is mandatory to study the urethra, ureter, the prostate in men, and radial margins (2).

6.3 Pathology of muscle-invasive bladder cancer

No cases of papillary urothelial neoplasms of low malignant potential and low-grade carcinoma are present in this stage. All cases are high-grade urothelial carcinomas (grade II or grade III in WHO 1973). For this reason, no more prognostic information can be provided by grading muscle-invasive bladder cancer (3).

However, some morphological subtypes can be most important for prognosis and treatment decisions, as in:

- small-cell carcinomas
- urothelial carcinomas with squamous and/or glandular partial differentiation
- spindle cell carcinomas
- some urothelial carcinomas with trophoblastic differentiation.

For staging, TNM 2002 is recommended. The pattern of muscular invasion can provide some prognostic information. Most cases show nodular or cordonal growth, but around 44% of cases are found to have an infiltrative pattern. According to some authors (3), the median survival time of an infiltrative pattern is lower than other pattern types ($p = 0.06$). Blood vessel invasion and lymph node infiltration have an independent prognostic significance (4). It seems that the pN category is closely associated with the number of lymph nodes studied by the pathologist. For this reason, some authors have observed that more than 9 lymph nodes have to be investigated to reflect pN0 appropriately.

New prognostic markers are under study. Only p53 combined with p27 might be useful, but the association with outcome is not completely proven (6).

6.4 GUIDELINES ON ASSESSMENT OF TUMOUR SPECIMENS

Mandatory evaluations

- Depth of invasion (categories pT2 vs pT3a, pT3b or pT4)
- Margins with special attention paid to the radial margin
- Histological subtype, if it has clinical implications
- Extensive lymph node representation (more than eight)

Optional evaluations

- Bladder wall blood vessel invasion
- Pattern of muscle invasion

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7. TREATMENT: CYSTECTOMY

7.1 Radical cystectomy

7.1.1 Background

Generally, radical cystectomy is the gold standard treatment in most countries for muscle-invasive bladder tumours. However, renewed interest in quality-of-life issues has increased interest in bladder preservation treatments (1,2). Urologists in certain countries, such as the USA and Germany, favour early cystectomy, while others, such as those in the UK (3), appear to use radiotherapy and/or chemotherapy as the first choice and reserve cystectomy for salvage treatment. Also, performance status and age can influence the choice of therapy, with cystectomy being reserved for younger patients without concomitant disease. In one population-based analysis, it was found that more than 60% of the patients with muscle-infiltrating tumours were considered unsuitable for radical cystectomy (4). Bladder-sparing surgery together with neoadjuvant or adjuvant chemotherapy and/or radiation may be a reasonable alternative to radical cystectomy.

7.1.2 Indications

The primary indication for cystectomy is muscle-invasive bladder cancer T2-T4a, N0-NX, M0. Other indications are high-risk superficial tumours (T1 G3 and BCG-resistant Tis) and extensive papillary disease that cannot be controlled with conservative measures. Whether p53 can help select patients with pT1 tumours who may

benefit from early cystectomy remains controversial (5,6). Salvage cystectomy is indicated for non-responders to non-surgical therapies or relapse after bladder-sparing treatments, as well as for non-transitional cell carcinomas, as these tumours generally respond less well to chemotherapy and radiotherapy than TCC. Contra-indications for cystectomy are major co-morbidity and patients not willing to accept the surgical risks. The overall staging error between clinical and pathological stages was as high as 44% in one series (7) and has been found to be highest for tumours in the T2 category (8). The frequency of regional lymph node metastases depends on the T-stage, ranging from less than 10% in T1 to almost 33% in the T3-T4 category.

7.1.3 *Technique*

Radical cystectomy consists of removal of the bladder and neighbouring organs, such as the prostate and seminal vesicles in men and uterus and adnexa in women. The distal part of the ureters is also usually resected and in cases with CIS, a frozen section of the margin is advisable. The indications for urethrectomy are controversial and have been reduced presumably because of the advent of bladder substitution. Currently, urethrectomy is recommended if the tumour involves the bladder neck in women (8) and the prostatic urethra in men. Recent reports indicate that the decision to perform urethrectomy may be based on the results of a frozen section of the urethral margin; however, these studies are hampered by their short follow-up times (10,11). The urethra may also be excised as a secondary procedure. Studies suggest that radical cystectomy with preservation of sexual function can be performed in some men (12).

Radical cystectomy also includes a dissection of the regional lymph nodes, which can give valuable prognostic information. There are several issues regarding this procedure, including the intention, the anatomical extent and the impact on the remaining operative procedure of the lymphadenectomy. Is the intention of this procedure diagnostic or curative? Its use in the diagnostic setting has been based on the poor prognosis of patients with positive nodes. Its therapeutic effect has not been fully documented. There are some reports of a relatively good prognosis in cases with very limited lymph node involvement and this has stimulated the proponents of curative dissection (13). The limited lymph node dissection consists of removing the tissue in the obturator fossa. Others (14,15) favour extended lymphadenectomy with removal of the obturator, internal, external and common iliac nodes, the presacral nodes, and the lymph nodes at the aortic bifurcation. They reported that extended lymphadenectomy improved survival in patients with tumours confined to the urinary bladder.

The results of lymph node staging can influence how the procedure is completed. Those who favour a frozen section will change the rest of the operation if positive nodes are verified, e.g. no cystectomy will be performed or a simpler type of urinary diversion will be chosen. The other group argue the pitfalls of frozen sections and the advantage of tumour debulking with respect to the patient's quality of life. No controlled studies exist supporting the curative value of lymph node dissection, thus only limited dissection is recommended.

7.1.4 *Morbidity and mortality*

The operative mortality has decreased during the last few decades; it was 3.7% in the European Organization for Research and Treatment of Cancer (EORTC) Medical Research Council (MRC) trial (16) and 2.3% and 1.2% in the Nordic Cystectomy trials I and II, respectively (17). Early morbidity is around 30% (18,19) and is usually transient. Late morbidity is mainly due to the urinary diversion. The risk of impotence is high and age dependent (20).

7.1.5 *Survival rates*

The 5-year survival rate is usually reported to be in the range of 40-60% and has not improved significantly in recent times. The use of pre-operative radio- or chemotherapy has not changed the outcome. In a recent report, the 5-year survival rates with no pre-operative therapy were 75% for stage pT1, 63% for stage pT2, 31% for stage pT3 and 21% for stage pT4 disease (21). Approximately 10% of cystectomy specimens are without tumour (stage pT0) due to radical TUR. Whether or not this confers a survival advantage is controversial (22,23). Tumour stage and nodal involvement are the only independent predictors of survival (24). P53 overexpression and mutation do not appear to be superior to staging as prognostic markers (25,26).

7.2 **RECOMMENDATIONS**

1. Radical cystectomy in T2-T4a, N0-NX, M0 and recurring T1 G3 and Tis.
2. No pre-operative radio- or chemotherapy.
3. Limited lymph node dissection.
4. Preservation of the urethra if margins are negative.

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7.4 Urinary diversion after radical cystectomy

Four treatment options are presently considered after cystectomy: an ileal conduit; a continent pouch; a bladder reconstruction; or ureterosigmoidostomy. The long-term quality of life outcomes for patients with the first three options, which are the major approaches, have recently been studied (1-3). Regardless of the type of urinary diversion, the majority of patients reported good overall quality of life, little emotional distress and few problems with social, physical or functional activities. Problems with urinary diversion and sexual functioning were identified as being the most common. No prospectively controlled randomized studies between the major alternatives have been performed. Bladder reconstruction seems to have become the first option in many centres.

Contra-indications to more complex procedures are debilitating neurological and psychiatric illnesses, short life expectancy and impaired liver or renal function. Patients undergoing continent urinary diversion have to have the motivation and skill to learn self-catheterization. Contra-indications to orthotopic bladder substitutes are TCC of the prostatic urethra, widespread CIS, high-dose pre-operative irradiation, complex urethral stricture and intolerance to incontinence.

7.4.1 *Ileal conduit*

The ileal conduit is a reliable treatment option with established efficacy. After long-term follow-up, however, 20% of patients develop stomal complications and 30% of the renal units become dilated (4). The disadvantage of the ileal conduit is mainly cosmetic.

7.4.2 *Conventional ureterosigmoidostomy*

This procedure became obsolete due to a high incidence of upper urinary tract infections and the risk of developing malignancy in the bowel. Bowel frequency and urge incontinence were also common. Recent modifications have been reported to decrease these complications, however, and the procedure has become a standard option in selected centres (5,6).

7.4.3 *Continent pouch*

The continent pouch operation has become a routine procedure during the last two decades. The introduction of three processes were essential for its development:

- The principle of bowel detubularization to create a low-pressure reservoir in the form of a balloon-shaped sac
- An anti-reflux and continence mechanism
- The use of self-catheterization

A variety of continent reservoirs have been introduced; the majority use ileal segments, ileocaecal segments or the sigmoid colon (7). Following continent urinary diversion, early and late complications have been encountered in 12% and 37% of patients, respectively (8). Late complications include ureteral stricture/obstruction, incontinence, difficulty in catheterization and urinary stones. Metabolic complications are common, but in the majority of cases, and with correct patient selection and education, problems may be minimized with the use of an appropriate bowel segment and early intervention (9). The remaining disadvantage is that a stoma is still necessary.

7.4.4 *Bladder reconstruction*

Bladder reconstruction or the orthotopic bladder operation has been performed in men for more than a decade, and also, more recently, in women. The reservoir is anastomized to the top of the urethra and the main advantage is that no stoma is necessary. The patient empties the bladder by abdominal straining or clean intermittent catheterization. Disadvantages include nocturnal leakage and problems with voiding requiring intermittent self-catheterization (10). The patient empties the bladder by abdominal straining and usually regains daytime continence while nocturnal leakage remains a problem. Increased post-void residual urine is initially rare, but is reported to affect almost half of the patients after long-term follow-up (11). This is managed by clean intermittent catheterization.

7.5 GUIDELINES ON URINARY DIVERSION AFTER RADICAL CYSTECTOMY

1. Treatment is recommended at centres with experience in the major types of diversion techniques. These operations should be centralized to departments doing cystectomies on a regular basis.
2. Patients planned for cystectomy should be informed of the possible alternatives, and the final decision has to be based on a consensus between patient and surgeon.

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8. TREATMENT: DEFINITIVE RADIOTHERAPY

Two types of patients with bladder cancer must be discriminated from each other when comparing survival after radiotherapy with survival after total cystectomy.

- Firstly, patients who are candidates for total cystectomy, but who are offered primary radiotherapy for bladder preservation, with salvage cystectomy in case of persistent disease. No modern trial has so far compared this strategy with primary total cystectomy.
- Secondly, patients in whom total cystectomy is not a therapeutic option either due to locally advanced disease (T4b, eventually T3B) or high age, major co-morbidity and/or decreased performance status.

Furthermore, results from curatively intended radiotherapy must be differentiated from those associated with palliative therapy.

8.1 External beam radiotherapy

The target field usually comprises the bladder only, with a safety margin of 1.5-2 cm, considering unavoidable organ movements. Any beneficial effect with larger pelvic fields has not been demonstrated. The target dose for curative radiotherapy of bladder cancer is 60-66 Gy, with a subsequent boost using external radiotherapy or interstitial brachytherapy. The daily dose is usually 1.8-2 Gy, and the course of radiotherapy should not extend beyond 6-7 weeks (1,2) to minimize the re-population of cancer cells.

The overall 5-year survival rates in patients with muscle-invasive bladder cancer are approximately 40-60%, with bladder-cancer-specific survival between 35% and 40%, with a local recurrence rate of approximately 30%. Based on older trial results, a recent Cochrane analysis (3) suggested an overall survival benefit with radical surgery versus radical radiotherapy in patients with muscle-invasive bladder cancer.

As well as the T category, important prognosticators for the outcome of radiotherapy include tumour size, presence of hydronephrosis, completeness of pre-radiation, transurethral resection of bladder tumour (TURB) and complete response to radiotherapy (4). Using modern standard radiotherapy techniques, major, radiation-related, late morbidity from the bladder and the bowel is less than 5% in tumour-free patients.

8.2 Interstitial brachytherapy

Patients with small T1/T2 tumours can be treated by implantation of radioactive sources (caesium, iridium) combined with external radiotherapy and bladder-preserving surgery (5). The reported survival rates range from 60-80%, depending on the T category.

8.3 Pre-cystectomy radiotherapy

There is no superiority of planned pre-cystectomy radiotherapy (6).

8.4 Radiotherapy and chemotherapy

Clinical studies of cisplatin-based chemotherapy combined with radiotherapy have demonstrated response rates of 60-80% with 5-year survival rates of 50-60% (7-11). Bladder preservation seems possible in 50% of patients. However, no definitive long-term results from randomized studies are available.

8.5 Radiosensitizers

Previous attempts to combine radiotherapy of the bladder with hyperbaric oxygen or misonidazole have not been successful, partly due to technical difficulties. More promising results have been obtained with a combination of accelerated radiotherapy with carbogen (ARCO) or carbogen nicotinamide (ARCON) (12,13), with approximately 60% 3-year survival rates as compared with approximately 30% after radiotherapy alone (12).

8.6 Palliation radiotherapy

Uncontrollable symptoms due to large bladder tumours (haematuria, urgency, pain) can be palliated by radiotherapy of short duration (7 Gy x 3; 3-3.5 Gy x 10) (14). However, such a fractionation pattern increases the risk of acute intestinal morbidity, including diarrhoea and abdominal cramps.

8.7 GUIDELINES ON RADIOTHERAPY

- Modern 3D-radiotherapy, with- or without chemotherapy or radiosensitizers, is a reasonable treatment option in patients who wish to preserve their bladder
- The requirements for success of such a strategy are:
 - A multidisciplinary approach within the responsible institution, involving co-operation between the urologist, radiotherapist, medical oncologist and pathologist
 - A regular follow-up schedule in order to perform salvage cystectomy in patients with recurrent disease as soon as possible

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9. TREATMENT: SYSTEMIC CHEMOTHERAPY

9.1 Introduction

Following cystectomy for muscle invasive bladder carcinoma, up to 50% of patients may develop metastases. Five-year survival rates of 36-54% have been reported in cystectomy series from major academic centres (1-4). For high-risk patients with pT3-pT4 and/or pN+M0 bladder cancer, the 5-year survival rate is only 25-35%. One-third of patients relapse in the pelvis alone, but most patients relapse in distant sites. Response rates of 40-70% have been seen with cisplatin-containing combination chemotherapy regimens. This level of response has led to their use for locally invasive disease in combination with cystectomy or radiotherapy, either as neo-adjuvant or adjuvant therapy.

9.2 Neo-adjuvant chemotherapy

Neo-adjuvant chemotherapy is intended for patients with operable stage T2-T4a muscle-invasive disease. Chemotherapy is given prior to cystectomy or radiation therapy to improve the survival rate in patients by treating micrometastatic disease. It has also been used in some programs to preserve the bladder (5). Systemic therapy is delivered early when the burden of metastatic disease is minimal, and is better tolerated prior to surgery or radiation. Neo-adjuvant therapy has less toxicity in patients with metastatic disease, since patients generally have a better performance status and localized disease.

Neo-adjuvant chemotherapy trials show either a trend towards a small benefit or no benefit. It is possible that the majority of trials may not have enlisted sufficient numbers of patients to detect statistically significant differences in survival.

The Medical Research Council (MRC) of the UK and the European Organization for Research and Treatment of Cancer (EORTC) have completed a large randomized neo-adjuvant chemotherapy trial. Patients were treated with cisplatin, methotrexate and vinblastine (CMV) followed by either cystectomy or radiotherapy versus immediate cystectomy or radiotherapy. (6). With a follow-up of 7.4 years (7), patients treated with CMV chemotherapy have shown a consistent survival benefit ($p=0.048$), which has been maintained with a 5-year survival rate of 44% versus 50% and an 8-year survival rate of 37% versus 43%.

A meta-analysis of 10 neo-adjuvant chemotherapy trials has been performed, (8). The overall survival for the whole group was not affected by neo-adjuvant chemotherapy. Patients treated with single-agent cisplatin did not benefit. A subgroup analysis of patients treated with combination chemotherapy suggested 5% (CI: 1-7%) activity in favour of neo-adjuvant chemotherapy. This advantage is not surprising, because the majority of patients were derived from the EORTC/MRC trial.

The USA Southwest Oncology Group (SWOG) Intergroup trial randomized patients similarly between three cycles of neo-adjuvant methotrexate, vinblastine, adriamycin and cisplatin (MVAC) chemotherapy prior to cystectomy versus cystectomy alone (9). The estimated risk of death was reduced by 25% (HR 1.33) (9). Median survival among those randomized to surgery alone was 46 months, compared to 77 months for patients who received MVAC ($p = 0.06$).

9.3 Neo-adjuvant chemotherapy and bladder preservation

Selected patients with invasive bladder tumours after neo-adjuvant chemotherapy may preserve their bladders, although the approach is highly controversial (5). Bladder preservation may be possible with an integrated approach using chemotherapy and radiotherapy. This combination is capable of producing 5-year survival rates between 42% and 63%, with organ preservation in approximately 40% of patients (10). Prognostic factors for local curability are small tumour size, absence of hydronephrosis, papillary histology, visible complete TURB and a complete response to induction chemotherapy. Randomized trials are needed to confirm these results.

9.4 Adjuvant chemotherapy

Several trials with combination chemotherapy appeared to show a difference in favour of chemotherapy. However, the results are controversial because of the small sample size and confusing analyses and methodology (11). Based on the desire to treat only patients who were truly at high risk, the EORTC together with several other international groups have begun a large adjuvant trial that will enlist 1,344 patients worldwide. The study will evaluate four cycles of immediate chemotherapy versus therapy at the time of relapse in high-risk patients with pT3-pT4 or node-positive disease. Three different chemotherapy regimens are permitted: MVAC, high-dose MVAC (HD-MVAC), and gemcitabine plus cisplatin (GC) (12-14).

Decisions concerning individual patients must be made after careful examination of the histological specimen and knowledge of the known relapse rates per pathological stage.

9.5 Metastatic disease

9.5.1 Chemotherapy protocols

Two prospective randomized trials have proven the superiority of MVAC (methotrexate, vinblastine, adriamycin

and cisplatin) over single-agent chemotherapy (15,16). Unfortunately, the use of cisplatin-based combination chemotherapy is associated with long-term survival in only approximately 15-20% of patients. The median survival duration is only 13 months. Long-term survival is attained in approximately 15% of patients with metastases in visceral sites and in 30% of those with nodal disease. Other therapeutic options and strategies are clearly needed.

The EORTC GU Group has compared a 2-weekly schedule of HD-MVAC to standard MVAC (13). A statistically significant difference in terms of complete remission rate and progression-free survival in favour of HD-MVAC was observed. Although no difference in median survival was seen, an increase in 2-year survival was observed. All the survival curves diverged in favour of the HD-MVAC treatment arm. However, this finding may have been due to the small number of patients in the tails of the curves.

Novel chemotherapeutic agents, such as gemcitabine and the taxanes, are among the most interesting therapeutic options currently available (17). In an international trial, MVAC was compared to GC (14). The overall survival rate was similar in both arms, as was time to progressive disease, time to treatment failure, and response rate.

More GC patients than MVAC patients had grade 3/4 anaemia and thrombocytopenia. More MVAC patients than GC patients had grade 3/4 neutropenia, neutropenic fever, grade 3/4 mucositis and alopecia. Quality of life was maintained during treatment in both arms. GC appeared to have a reduced toxicity profile compared to MVAC. This study was not statistically powered to reveal equivalence in terms of survival to MVAC, nor has GC been compared to HD-MVAC. Nonetheless, many clinicians have begun to use GC as another standard regimen.

The combination of gemcitabine and taxol has been shown to be highly effective in patients who have failed prior MVAC (18). When cisplatin, gemcitabine and taxol were given to untreated patients, high overall response rates were observed (19). The triplet is being compared to GC by the EORTC.

9.5.2 Prognostic factors

Prognostic factors that predict response to chemotherapy include alkaline phosphatase, age greater than 60 years, performance status and visceral metastases (16,20,21). Independent poor prognostic factors are Karnofsky performance status less than 80% and the presence of visceral (lung, liver, bone) metastases (21). Median survival times varied from 9 months in patients with two poor prognostic factors, to 13 months with one poor prognostic factor, and 33 months with no poor prognostic factors ($p = 0.0001$). For this reason, phase II trials can only reveal if a treatment is active or not, and if feasible or not. Careful prognostic factor analyses are important, but phase III randomized trials are more reliable as they tend to stratify patients according to the number of risk factors to avoid imbalance in treatment arms.

More recently, significant interest has developed in molecular markers, such as p53, Rb and p21, to help optimize therapy and predict chemosensitivity (22).

9.5.3 Conclusions

Muscle-invasive bladder cancer can be treated with chemotherapy. Response to neo-adjuvant chemotherapy is an important prognostic factor, but this may represent patient selection factors.

Whether it is best to give chemotherapy in the neo-adjuvant or adjuvant setting has not yet been clearly determined. Adjuvant studies in the literature have been less definitive than neo-adjuvant studies. The ability to evaluate molecular prognostic markers such as p53 have led to new, adjuvant chemotherapy trials.

9.6 GUIDELINES ON CHEMOTHERAPY

- Cisplatin-containing combination chemotherapy has resulted in complete remissions in 40-70% of patients, with cures in selected cases
- MVAC and GC are both used as up-front chemotherapy for metastatic disease. Median survival is 12-14 months
- A minimal survival benefit has been shown with neo-adjuvant chemotherapy before cystectomy or radiotherapy
- Neoadjuvant chemotherapy in combination with radiotherapy for the purpose of bladder preservation is an investigational approach
- Convincing data are not yet available on the benefits of adjuvant chemotherapy. Results of randomized adjuvant trials are pending

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10. QUALITY OF LIFE

The assessment of health-related quality of life (HRQL) in patients with cancer is based upon the evaluation of (at least) physical, emotional and social functions, using validated questionnaires, such as FACT (Functional Assessment of Cancer Therapy)-G (1), EORTC QLQ-C30 (2) or SF (Short Form)-36 (3). HRQL also includes the assessment of subjective morbidity according to cancer type, using psychometrically tested instruments, such as FACT-BL for bladder cancer. Most published studies in patients with bladder cancer are retrospective investigations performed using a cross-sectional design and do not evaluate the association between global

HRQL and specific prostatectomy (micturition problems, urinary leakage, skin problems, reduced body image and sexuality). Important confounders have only rarely been considered, such as timing (4), patient's age, personality, coping ability and cultural background (5).

In patients, who have been cystectomized for muscle-invasive bladder cancer, the general expectation among urologists was that continent bladder substitutes would result in HRQL superior to that after incontinent diversions (5-14). There has indeed been a gradual improvement of the above specific sequelae, but the expectations as to HRQL have not always been fulfilled with statistical significance, probably due to methodological problems (10) and/or the phenomenon of 'response shift' (15). Nevertheless, patients with a continent bladder-substitute generally score more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function (6,14). In one study (13), a statistically significant difference in clinical relevance was observed for HRQL in favour of neobladders.

HRQL is impaired in many patients with locally advanced bladder cancer that is not suitable for curative treatment because of associated micturition and sleeping problems and disturbance of social and sexual life (16). The relief of bladder-related symptoms is obtained by palliative surgery, radiotherapy and/or chemotherapy (17), though there is limited literature describing HRQL in palliatively treated bladder cancer patients (18-20).

Finally, HRQL parameters have recently been shown to represent independent prognostic parameter (21).

10.1 RECOMMENDATIONS FOR QUALITY OF LIFE IN BLADDER CANCER

- Prospective studies of HRQL in patients with bladder cancer should be initiated to explore the interaction between long-term morbidity specific to bladder cancer, response shift, coping and personality. Such studies benefit from co-operation between clinicians and experts experienced in HRQL assessment
- Pre-treatment, individualized and realistic counselling of the patient and his/her partner, the patient's participation in treatment decisions and application of the most effective and toxicity-sparing treatments are required to obtain optimal post-treatment HRQL in patients with bladder cancer

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11. FOLLOW-UP: AFTER TREATMENT WITH CURATIVE INTENT

11.1 Rationale for follow-up

Follow-up of patients with invasive bladder cancer after cystectomy and radiotherapy is recommended to detect local recurrence and distant metastases as early as possible to permit additional treatment when indicated and if possible. Such therapy may include salvage cystectomy, urethrectomy, nephro-ureterectomy and or systemic chemotherapy with and without secondary surgery for residual tumour. Moreover, side-effects of urinary diversion should be recognized early on and corrected if possible.

11.2 Principles

Prognostic factors and type of intervention (cystectomy, radiotherapy) are relevant in determining the most efficient follow-up regimen. The pT and pN-stage are the most important prognostic factors and in addition risk factors such as pTis will guide the follow-up procedures.

11.3 Follow-up Procedures

11.3.1 Cystectomy

The first assessment is at 3 months postoperatively and includes :

- Physical examination to exclude surgical complications
- Serum creatinine and blood gas analysis to assess kidney function
- Urine analysis
- Sonography of the kidney, liver and retroperitoneum
- Chest-X-ray

In case of unremarkable findings regular follow-up in intervals of 4 months are indicated. In case of pN+ additional regular CT scans and bone scintigraphy are necessary. PTis patients need regular assessment of the upper urinary tract. Barbotage cytology is recommended for the remaining urethra.

11.3.2 Radiotherapy

The first assessment is at 3 months post-radiotherapy and includes :

- Physical examination to exclude surgical complications
- Serum creatinine and blood gas analysis to assess kidney function
- Urine analysis
- Sonography of the kidney, liver and retroperitoneum
- CT scan of the pelvis
- Cystoscopy and urine cytology
- Chest-X-ray

The main interest during follow-up remains the bladder, because of the high local failure rate.

12. ABBREVIATIONS

This list is not comprehensive for the most common abbreviations

ARCO	accelerated radiotherapy with carbogen
ARCON	accelerated radiotherapy with carbogen nicotinamide
ASCO	American Society of Clinical Oncology
CIS	carcinoma in situ
CISCA	cisplatin, cyclophosphamide plus adriamycin
CMV	cisplatin, methotrexate plus vinblastine
EAU	European Association of Urology
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
GC	gemcitabine plus cisplatin
HD-MVAC	high-dose methotrexate, vinblastine, adriamycin plus cisplatin
HRQL	health-related quality of life
MRC	Medical Research Council (UK)
MVAC	methotrexate, vinblastine, adriamycin plus cisplatin
SCC	squamous cell carcinoma
SF-36	Short Form-36
SWOG	Southwest Oncology Group
TCC	transitional cell carcinoma
TNM	Tumour, Node, Metastases
TUR	transurethral resection
TURB	transurethral resection of bladder tumour
UICC	Union International Contre le Cancer
WHO	World Health Organization