Review

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Definitive Radiotherapy in Bladder Cancer

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Abstract

Bladder cancer is the most common cancer among urinary tract cancers; urothelial carcinoma accounts for 90% of the cases. The presence of muscle invasion in the specimen is a significant factor that worsens the prognosis and leads to radical changes in treatment. The management of non-metastatic disease is divided into two main groups: non-muscle invasive bladder cancer (NMIBC) and musle invazive baldder cancer (MIBC). The aim of this review is to provide information about the role, technique, dose-fractionation regimens, and toxicity of definitive radiotherapy in non-metastatic localized bladder cancer. Evaluating studies related to definitive radiotherapy in NMIBC suggests that there are potential benefits; however, the literature does not provide clear information regarding the role of radiotherapy. In MIBC patients, the radiotherapy regimen administered simultaneously with radiosensitizing chemotherapy following maximal transurethral resection is referred to as trimodal therapy (TMT). The role of definitive radiotherapy in the MIBC group is clearer. Although there is no randomized study directly comparing TMT with radical cystectomy, TMT applied after careful patient selection has emerged as an effective treatment method that provides treatment success comparable to radical cystectomy. Adding concurrent chemotherapy to curative radiotherapy increases disease control rates. The most commonly used and currently recommended first-line agent in concurrent therapy is cisplatin. Conventional fractionation, hypofractionation, or accelerated hyperfractionation treatments may be preferred. The most commonly used conventional fractionation regimen is 45-46 Gy to the pelvis at 1.8-2 Gy daily, followed by 63-66 Gy to the bladder with a concomitant boost. The inclusion of pelvic lymph nodes in curative radiotherapy remains a controversial topic. The use of intensity-modulated radiotherapy provides dosimetric advantages over three-dimensional conformal radiotherapy and leads to a decrease in side effects. Follow-up after TMT is crucial for the early detection of local and distant recurrences and for monitoring treatment-related toxicity.
Keywords: Bladder cancer, trimodal therapy, radiotherapy

Introduction

Bladder cancer, the most common cancer among urinary tract cancers, accounts for approximately 3% of all cancers. It is the 6th most common cancer in terms of incidence in the United States. Risk factors for the disease include male sex, advanced age, smoking, and occupational carcinogens. Schistosoma infection is also a significant risk factor in African and Middle Eastern countries. The disease is four times more common in men than in women, and 90% of those diagnosed are aged 55 and older. Smoking and occupational carcinogens are the most important risk factors for the disease (1-3). Urothelial carcinoma [transitional cell carcinoma (TCC)] constitutes 90% of bladder cancer cases, while the remaining pathologies include squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. The most important symptom of the disease is painless hematuria. Cystoscopy and transurethral resection (TUR) are the gold standards for the definitive diagnosis and staging of the disease (4-6). TUR is also important as it forms the initial phase of the treatment process. The muscle layer must be present in the TUR specimen when staging the disease. The presence of muscle invasion in the specimen is a critical step in the management of the disease. Muscle invasion is a significant factor that worsens the prognosis and necessitates radical changes in treatment (5-7). The management of non-metastatic disease is divided into two main groups: non-muscle invasive bladder cancer (NMIBC) and musle invazive baldder cancer (MIBC). In MIBC, the risk of systemic recurrence is high, and the 5-year survival rate is around 50-60% (4). In this review,

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we aim to provide information about the site, technique, dose-fraction regimens, and toxicity of definitive radiotherapy in non-metastatic localized bladder cancer.

Definitive Radiotherapy in Bladder Cancer

The staging of non-metastatic bladder cancer is based on muscle layer invasion. Muscle invasion necessitates radical changes in the management of the disease (5-8), therefore, definitive radiotherapy for non-metastatic bladder cancer can be considered in two main groups: NMIBC and MIBC.

Definitive Radiotherapy in Non-muscle Invasive Bladder Cancer

The diagnosis, staging, and initial treatment process of bladder cancer primarily involve TUR. In addition to being a significant risk factor for bladder cancer, smoking is also a factor that increases the risk of recurrence and progression of the disease; therefore, smoking cessation should be recommended in every patient diagnosed with bladder cancer (7,8). Ta, T1, and carcinoma *in situ* (CIS) are classified within the NMIBC group. Patients diagnosed with NMIBC are categorized into 3 classes: low, intermediate, and high risk according to the results obtained in TUR. The classification of risk groups determines the treatment approach following TUR. Factors considered in risk classification include whether the tumor is primary or recurrent, tumor number, size, T stage, presence of concurrent CIS, and grade. Scoring systems developed by European Organisation for Research and Treatment of Cancer (EORTC) are also available to assess the risk of recurrence and progression in NMIBC (9). These scoring systems take into account the factors analyzed in risk classification; if a lesion recurs, the time to recurrence (≤1 year vs. >1 year) is also considered. According to the EORTC recurrence score, patients can score between 0 and 17, with those scoring <5 being considered to have a low recurrence score. Patients with a single tumor, primary tumor, TaG1, <3 cm, and no CIS are classified as low risk, while those with T1, G3, or any of the CIS factors are classified as high risk. Patients who do not fall into these two groups are classified as intermediate risk (8). Following TUR, patients classified as low risk are recommended to receive one dose of intravesical chemotherapy. For intermediate-risk patients, intravesical Bacillus Calmette-Guérin (BCG) for one year or intravesical chemotherapy for a maximum of one year is recommended. High-risk patients are advised to undergo 1 to 3 years of full-dose intravesical BCG. Within the high-risk group, patients with T1G3 + concurrent CIS, multiple or recurrent T1G3, T1G3 + CIS in the prostatic urethra, certain forms of urothelial carcinoma, or positive lymphovascular invasion are regarded as the highest risk group. Radical cystectomy should be considered for this patient group (7,8).

In the primary treatment of NMIBC, TUR and intravesical therapies play a leading role, while there are limited studies regarding the role of radiotherapy (10-12). Notably, the majority of these limited studies are retrospective (11). In a randomized study, radiotherapy was compared to observation or intravesical treatment in patients with T1G3 TCC. The results indicated that radiotherapy did not improve progression-free survival compared to the observation, or intravesical treatment groups (10). In a prospective study, radiotherapy or chemoradiotherapy was administered after maximal TUR to patients with T1G3 and T1G2 + CIS and/or multifocal and/or tumors >5 cm and/or multiple recurrent TCC. In this study, which involved 141 patients, the median follow-up duration was 62 months. Treatment response assessment was conducted at the 6th week post-radiotherapy using TUR. In cases of persistent disease or progression after a complete response, salvage cystectomy was recommended. A complete response was observed in 88% of patients. The 5- and 10-year tumor progression rates were found to be 19% and 30%, respectively. The 5- and 10-year disease-specific survival rates were 82% and 73%. More than 80% of surviving patients retained their bladder, and 70% reported satisfaction with bladder function. In another prospective study, patients with T1G3 TCC underwent chemoradiotherapy after TUR (13). This study included 64 patients, with a median follow-up of 43 months. TUR was performed to evaluate treatment response after chemoradiotherapy. A complete response was observed in 90.2% of patients. The 5-year overall and disease-specific survival rates were found to be 76% and 93%, respectively. During follow-up, two patients underwent cystectomy due to a shrinking bladder. The study emphasized that multimodal treatment is a safe and effective treatment for patients with T1G3 TCC. While radiotherapy may have benefits in NMIBC, the data do not provide clear information about its role; therefore, randomized prospective studies are needed.

Definitive Radiotherapy in Muscle Invasive Bladder Cancer

Patients with non-metastatic disease classified as T2 and above based on TUR pathology are referred to as MIBC. The standard approach for MIBC patients is neoadjuvant chemotherapy followed by radical cystectomy and pelvic lymph node dissection (14,15). Neoadjuvant chemotherapy has been shown to contribute to survival in patients undergoing radical cystectomy (14). Recommended regimens for neoadjuvant chemotherapy include dose-dense methotrexate, doxorubicin, and cisplatin (ddMVAC) or gemcitabine and cisplatin chemotherapy. For patients ineligible for cisplatin, adjuvant ddMVAC or one of the gemcitabine and carboplatin chemotherapy regimens is recommended following direct surgery. Furthermore, studies regarding the use of immunotherapy agents, particularly nivolumab, in this patient group and in ypT2-ypT4a or ypN+ patients after neoadjuvant treatment are ongoing (15). A significant number of bladder cancer patients are elderly and have comorbidities, or some may refuse procedures like radical cystectomy, which could result in morbidity and mortality. This means that many are not candidates for radical cystectomy. Radical cystectomy is a major surgical procedure that can lead to morbidity and mortality. Post-operative complication rates can reach up to 60%, and the 90-day postoperative mortality rate can range from 2%-13%. It has been reported that 60% of MIBC patients are not suitable for radical cystectomy at the time of diagnosis (16). For patients who cannot undergo radical cystectomy, the bladder-preserving trimodal therapy (TMT) approach is preferred as a curative treatment. In the TMT approach, the patient receives maximal TUR followed by curative radiotherapy and concurrent radiosensitizing chemotherapy. For appropriate patients, cisplatin is the first choice for concurrent

chemotherapy. The contribution of neoadjuvant or adjuvant chemotherapy in the TMT regimen has not been demonstrated. Patients with solitary cT2 without extensive CIS component, tumor <5 cm, macroscopic complete TUR, and without hydronephrosis constitute the ideal patient group for TMT (16).

The phase 2 study by Kragelj et al. (17) involved 84 MIBC patients who underwent concurrent radiotherapy with vinblastine-based chemotherapy following maximal TUR. A dose of 46-46.2 Gy was defined for the pelvis and 63.8-64 Gy for the bladder, with a daily fraction dose of 1.8-2.2 Gy. Radiotherapy was administered using the four-field box technique. Although the 9-year local control rate of 55% was found to be an encouraging result, the 9-year grade 3-4 side effect prevalence of 66% warns of side effects. In Gogna et al. (18) phase 2 study, 113 patients received concurrent radiotherapy with cisplatin-based chemotherapy after maximal TUR. A total dose of 63-64 Gy was administered, excluding elective lymph nodes from treatment. Acute grade 4 pelvic toxicity was not observed, while acute grade 3 urinary toxicity occurred in 23% of patients. At the 6-month post-treatment cystoscopic evaluation, 70% of patients achieved a complete response. Local invasive recurrence was found in 14% of patients (11/79) and a 5-year local control rate of 45%. Notably, 61% of patients continued to live with a functional bladder, and the 5-year disease-specific survival rate was reported at 50%. The study concluded that concurrent chemoradiotherapy based on cisplatin offers an effective response rate and is a tolerable treatment option for MIBC patients. In the phase 2 study conducted by Lagrange et al. (19) 51 patients were evaluated. Patients were included in the CRT protocol after TUR. After 45 Gy pelvic radiotherapy, a boost of 63 Gy was administered to the bladder. Cisplatin and 5-fluorouracil (5-FU) were administered as concurrent chemotherapy. Among patients receiving chemoradiotherapy, cystoscopic evaluation was performed after receiving 45 Gy in those who were suitable for radical cystectomy. Patients who did not show a complete response in this evaluation were accepted for cystectomy. In this study with a median follow-up of 8 years, the bladder preservation rate was 67%. The 8-year local control rate was also 67%. The quality of life score was found to be satisfactory, as a result of the study. The study demonstrated that multimodal treatment is effective, allowing 2/3 of the MIBC patient group to live with a functional bladder.

In a prospective study conducted by Zapatero et al. (20) 80 MIBC patients were divided into two treatment arms. Following maximal TUR, one group received neoadjuvant chemotherapy followed by 60 Gy of radiotherapy, while the other group received 64.8 Gy radiotherapy concurrently with cisplatin. At a median follow-up of 6 years, 83% of patients were found to continue living with their bladders. Although there were no significant differences between the two treatment groups in terms of overall survival and cancer-specific survival rates, the complete response and disease-free survival rates were significantly higher in the concurrent treatment group. Housset et al. (21) conducted a prospective study where patients received bifractionated split-course radiotherapy with 5-FU and cisplatin after TUR. In a cohort of 54 patients, response assessment was performed via control cystoscopy 6 weeks after concurrent treatment. Patients with persistent tumors were directed to cystectomy, while those with a complete response received additional chemoradiotherapy (group A) or cystectomy (group B). The complete response rate after control cystoscopy was 74%. The 3-year disease-free survival rate was 62%, which was significantly higher in the complete response group (77%) compared to the rate in those without complete response (23%). There were no differences in overall survival between groups A and B. The study emphasized that chemoradiotherapy is an effective and safe treatment modality that offers high response rates. In the study by Shipley et al. (22) 190 patients received concurrent radiotherapy with cisplatin-based chemotherapy following TUR. Response evaluation was conducted using biopsy and urine cytological analysis after 40 Gy. A complete response was identified in 121 patients. Patients with complete responses and those not suitable for cystectomy received a boost of 64-65 Gy of chemoradiotherapy. In total, 41 out of 66 patients (35%) underwent cystectomy due to lack of complete response, and 25 patients due to recurrent tumor. None of the patients underwent surgery due to treatment-related morbidity. Five and 10-year overall survival and disease-free survival rates were 54% and 36%, and 63% and 59%, respectively. The median follow-up period was 6.7 years, and the pelvic recurrence rate was 8.4%. It was stated that the survival data obtained were similar to those of surgical series. The TMT approach, incorporating tumor response assessment, is emphasized as a reliable treatment modality that allows most patients to live with a functional bladder. In James et al. (23) phase 3 study, 360 MIBC patients, were divided into radiotherapy or concurrent chemoradiotherapy groups. The concurrent chemotherapy included 5-FU and mitomycin C. The 2-year locoregional disease-free survival rate was significantly higher in the chemoradiotherapy group (67% vs. 54%). The 5-year overall survival rates were 48% and 35%, respectively. A decreasing trend was noted in the 2-year cystectomy rates in the chemoradiotherapy group, from 16.8% to 11.4%. Although long-term grade 3-4 side effects were slightly higher in the chemoradiotherapy group, the difference was not statistically significant (15.7% vs. 8.3%, p=0.07). The study concluded that adding concurrent chemotherapy to curative radiotherapy for bladder cancer enhances locoregional control without significantly increasing the side effects. Important prospective studies related to curative radiotherapy for MIBC are presented in Table 1.

Adding concurrent chemotherapy to curative radiotherapy for bladder cancer has been shown to increase disease control rates (23,24). It is known that adding neoadjuvant chemotherapy before radical cystectomy provides a survival benefit of about 5%. The contribution of neoadjuvant chemotherapy in patients undergoing TMT has also been investigated (25,26). In a large randomized trial, a comparison was made between a group receiving standard trimodality therapy (TMT) and a group that received two cycles of neoadjuvant methotrexate, cisplatin, vinblastine before TMT (25). The study was prematurely terminated due to a high rate of severe toxicity. Only 74% of patients were able to complete the treatment protocol. No significant differences were found between the two groups in terms of complete response, metastasis-free survival, or overall survival. A prospective study involving 348 patients

also demonstrated that adding neoadjuvant chemotherapy to TMT did not contribute to survival outcomes (26). Overall, the evidence suggests that adding neoadjuvant chemotherapy to TMT does not improve disease outcomes (24-26). The potential benefits of adding adjuvant chemotherapy to TMT have also been explored (27,28). However, completion rates for treatment with adjuvant chemotherapy were found to be low, and grade 3-4 toxicity rates were significantly high (28). Currently, due to a lack of level 1 evidence demonstrating the benefits of adding either neoadjuvant or adjuvant chemotherapy to TMT, the use of these treatment modalities in bladder-sparing approaches is not recommended (24).

While phase 2 and 3 studies have established the effectiveness of the TMT approach for MIBC, a noticeable gap exists in randomized controlled trials that compare TMT with radical cystectomy (24). This gap hinders a direct comparison of these two curative treatment modalities in MIBC management. A review indicated that among MIBC patients undergoing TMT, the 5-year disease-specific survival rate ranged from 50% to 82%, while the 5-year overall survival rate varied between 36% and 74%. The rate of salvage cystectomy in this patient group was between 25% and 30%. Additionally, the recurrence rates – both muscle-invasive and non-invasive – among patients achieving a complete response post-treatment ranged from 24% to 43% (24). Although survival outcomes of radical cystectomy series were slightly higher in comparison to the TMT series, it has been noted that these series may have included patients who were more suitable for surgery, potentially introducing bias. The lack of randomized controlled trials that directly compare TMT with radical cystectomy prevents a definitive assessment of the superiority of these treatment modalities. Considering the available studies and systematic reviews, TMT, when applied to carefully selected patients with MIBC, demonstrates treatment success comparable to that of radical cystectomy, while also offering effective bladder preservation for the majority of patients.

Radiotherapy Technique, Field, Dose/Fraction Regimes, and Toxicity in Bladder Cancer

In definitive radiotherapy for bladder cancer, the inclusion of pelvic lymph nodes in the treatment field is a controversial issue (16). A phase 3 study conducted by Tunio et al. (29) which involved 230 patients with MIBC, in which participants were divided into two groups: those with pelvic lymph node involvement and those receiving treatment solely for the bladder. The results indicated no significant differences between the two groups in terms of bladder preservation rates, disease-free survival, or overall survival. In Gogna et al. (18) study, pelvic lymph nodes were excluded from the treatment field in patients undergoing chemoradiotherapy. Goldsmith et al. (30) research, involving 315 patients, revealed that 26% of clinically lymph node-negative patients were found to have pathological lymph node positivity after surgery. Notably, approximately half of these cases showed positivity in the common iliac lymph nodes. These findings suggest that applying extended pelvic radiotherapy to include the common iliac region may be beneficial for MIBC patients. However, it is important to note that this study was conducted from 1987 to 2010, and the methodology for clinical staging was not clearly defined.

With the widespread use of modern imaging techniques such as positron emission tomography/computed tomography (CT), it is now becoming feasible to reduce the incidence of occult lymph node metastases. The Radiation Therapy Oncology Group (RTOG) guidelines recommend considering the treatment of pelvic lymph nodes. The decision to include or exclude the pelvic lymph nodes in bladder cancer radiotherapy varies according to clinical protocols and remains controversial. The National Comprehensive Cancer Network (NCCN) guidelines state that including the pelvic field should be optional and determined based on the patient's comorbidities and the risk of radiation-related toxicity (31).

In phase 3 studies conducted by Housset et al. (21) and Shipley et al. (22) split-course chemoradiotherapy was utilized. This approach involves performing a cystoscopic evaluation after administering 40-45 Gy. Patients achieving a complete response receive an additional radiation dose of 60-65 Gy, while those not responding are referred for surgery. The aim of split-course radiotherapy is to identify non-responders earlier in the treatment process, thereby sparing them from radiation toxicity. In contrast, continuous-course radiotherapy offers the advantage of completing treatment in a shorter timeframe. Unfortunately, there is no randomized study comparing these two radiotherapy regimens (16).

In studies related to radiotherapy for bladder cancer, various regimens have been utilized, including conventional, hypofractionated, hyperfractionated, and accelerated treatments (24,32-34). RTOG studies have employed accelerated hyperfractionated regimens (30). In a prospective study by Horwich et al. (33) 229 patients were divided into two groups: those receiving accelerated fractionated treatment and those receiving conventional treatment. In the accelerated fractionated regimen, a dose of 60.8 Gy/32 fractions was delivered. Treatment was applied in 2 sessions daily with a minimum of 6 hours between sessions. In the conventional regimen, 64 Gy/32 fractions were applied. Although there was no significant difference in local control between the groups, acute gastrointestinal side effects were found to be higher in the accelerated group. There is no randomized study directly comparing hyperfractionated radiotherapy to conventional radiotherapy; however, existing studies suggest that both regimens have similar efficacy. The hyperfractionated regimen is less commonly applied due to its lower feasibility in clinical practice. In a phase 2 study, concurrent hypofractionated radiotherapy with gemcitabine was applied to patients with MIBC after TUR, delivering a dose of 52.5 Gy/20 fractions (34). Post-treatment cystoscopic evaluations showed a complete response in 88% of patients, with a 3-year cancer-specific survival rate of 82%. The study emphasized that concurrent chemoradiotherapy with gemcitabine offers a high response rate with acceptable toxicity. James et al. (23) phase 3 study also utilized a hypofractionated regimen, where either 64 Gy/32 fractions or a dose scheme of 55 Gy/20 fractions was chosen. In a meta-analysis, hypofractionated and conventional regimens were compared in terms of toxicity and invasive locoregional control results (35). In this study, 782 patients were treated with 55 Gy/20 fractions as a hypofractionated regimen and 64

Gy/32 fractions as the conventional regimen. After 120 months of follow-up, the hypofractionated arm was found to be non-inferior in terms of toxicity and superior in terms of invasive locoregional control. The NCCN guideline states that accelerated hyperfractionated, conventional, or hypofractionated regimens can be preferred in definitive radiotherapy of MIBC (31).

In studies, definitive radiotherapy typically involves administering a dose of 45-46 Gy to the pelvis with a daily dose of 1.8-2 Gy, followed by a boost to the bladder, increasing the total dose to 63-66 Gy (16-27). A retrospective study evaluating dose escalation compared the outcomes of conventional fractionation doses of 60-66 Gy with those of 67-70 Gy doses (36). No significant difference was found between the two groups in terms of 2-year overall survival, however, patients receiving 60-61 Gy had lower overall survival compared to those receiving 64-66 Gy. The study concluded that doses of 62-66 Gy should be considered standard. In a phase 3 study involving 219 patients, participants were divided into groups receiving standard whole bladder radiotherapy and reduced high-dose volume radiotherapy (37). No significant differences in late toxicity were noted between the groups after 2 years of follow-up. The reduced high dose volume group was not shown to be noninferior to the standard group in terms of locoregional control. A retrospective study involving 26 patients compared whole bladder radiotherapy with partial bladder radiotherapy (38). In the whole bladder treatment group, 45-50.4 Gy was delivered to the pelvis and bladder with a daily dose of 1.8 Gy, followed by a 19.8-21.6 Gy boost to the whole bladder. In the partial bladder treatment group, pelvic lymph nodes received 45-50 Gy with a daily dose of 1.8-2 Gy, while the partial bladder received 55-62.5 Gy with a daily dose of 2.2-2.5 Gy, with simultaneous integrated boost technique. In this study, conventional fractionation and hypofractionation regimens were also compared. No significant difference was found between the groups in terms of local control, overall survival, and toxicity rates. The NCCN guidelines recommend a dose of 39.6-50.4 Gy for the whole bladder using either conventional fractionation or accelerated hyperfractionation, followed by a boost to 60-66 Gy to either the whole or partial bladder. Apart from this dose-fractionation regimen, it is also stated that a dose of 55 Gy/20 fractions can be applied to the entire bladder (31). As demonstrated, all three fractionation methods are included in the NCCN guidelines.

The treatment completion rate for TMT is reported to be high, ranging from 80% to 90%, and it is regarded as a tolerable treatment modality. In James et al. (23) phase 3 study, the rate of RTOG grade 3-4 side effects in the chemoradiotherapy group was 3.3% in the first year. The acute toxicity rates associated with TMT ranged from 10% to 36% (16,24), with gastrointestinal and urinary side effects being the most common. Grade 3 and higher side effects are extremely rare. Studies have also shown that the rates of late toxicity related to TMT are very low (16,24,39). Late effects may include symptoms such as urgency, nocturia, dysuria, and proctitis. In a study involving 285 patients utilizing data from four RTOG prospective study protocols, it was revealed a grade 2 pelvic toxicity rate of 10.2% (39). The rate of grade 3 and above genitourinary side effects was 5.7%, whereas the rate of gastrointestinal side effects was 1.9%. No grade 4 late toxicity or treatment-related deaths were observed. No patient underwent cystectomy due to treatment-related toxicity. Overall, based on the studies conducted, TMT stands out as a highly tolerable treatment modality with low rates of serious toxicity (16,23,24,39).

Various radiotherapy planning techniques have been employed in bladder cancer radiotherapy (40-43). In Zelefsky et al. (40) study involving 1,571 patients, the toxicities of patients planned with three-dimensional conventional radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) techniques were compared. After a 10-year follow-up, the rates of grade 2 and above gastrointestinal side effects were significantly lower in the IMRT arm (5-13%). In Søndergaard et al. (41) study, the dose-volume histogram of 16 bladder cancer patients treated with IMRT was compared with those treated with 3D-CRT (41). The study revealed that, the bowel volume exposed to these doses (V20, V25, V30, etc.) was lower in the IMRT group for 20 Gy, 50 Gy and all doses within this range the maximum doses to the rectum, V50, and V60 values were also found to be lower in the IMRT group. In another study by Søndergaard et al. (42) 116 patients treated with IMRT or 3D-CRT were compared in terms of side effects. This study found that the rate of diarrhea of acute grade 2 and above in the IMRT group was significantly lower than in the control group (30-56%). However, no significant differences were found in late toxicity rates between the groups. In another study, IMRT plans were compared with 3D-CRT plans in 19 patients (43). In this study, a total dose of 64.8 Gy was defined by delivering 45 Gy to an empty bladder followed by a boost dose of 19.8 Gy to a full bladder. Cone beam computerized tomography (CBCT) was used as an image-guided radiotherapy (IGRT) modality in this study. During the first phase, weekly CBCT scans were performed, whereas daily CBCT scans were performed during the boost phase. The analysis revealed that V40, V45, V50, V55, and V60 values for the rectum and bowel were lower in the IMRT arm. The irradiated bladder volume was also significantly lower in the IMRT arm. The median three-dimensional shift observed in the CBCT during the boost treatment was 0.62 cm. During the boost treatment planned for a full bladder, it was noted that the bladder was not completely full, and significant daily variations in bladder volume were detected. Utilizing IMRT in the radiotherapy of bladder cancer provides dosimetric advantages over 3D-CRT and reduces the rates of treatment-related toxicity (39-43). Given the challenges in consistently ensuring the same bladder volume, position, and the position of the adjacent organs, using CBCT as an IGRT method is crucial for the accurate delivery of radiotherapy.

Chemotherapy Regimens in Chemoradiotherapy

Adding concurrent systemic therapy to definitive radiotherapy for bladder cancer has been shown to increase disease control rates. Cisplatin is the most commonly used agent for concurrent systemic therapy. Its radiosensitizing properties render it a suitable agent for concurrent treatment (16,23,24). Literature indicates that, in addition to cisplatin monotherapy, cisplatin-based combination regimens have also been utilized for concurrent therapy. However, cisplatin-based combination regimens are associated with high toxicity. Regimens such as cisplatin +5-FU and cisplatin + docetaxel have been evaluated in various studies (16,19,21,24). Besides cisplatin and cisplatin-containing combinations, agents such as 5-FU, 5-FU + mitomycin C, weekly vinblastine, and low-

dose gemcitabine have also been administered concurrently with radiotherapy (16,17,24). Despite the absence of phase 3 randomized trials directly comparing non-cisplatin and cisplatin-based regimens, at present, cisplatin remains the first-choice agent for concurrent therapy in patients with adequate renal function (16,24,31).

Surveillance After TMT

Close surveillance after TMT is crucial for the early detection of local and distant recurrences, as well as for monitoring treatment-related toxicity (44). Even after successful treatment, the rate of invasive and non-invasive recurrences ranges from 24% to 43% (14,24). Recurrences are reported to be more frequent within the first two years (44). Although there are various follow-up protocols after TMT, the majority emphasize the importance of cystoscopic examination along with abdominopelvic and thoracic imaging (31,44). The NCCN guidelines recommend performing cystoscopic examinations every three months for the first two years, every six months for the next two to four years, and annually after the fourth year. The guidelines also suggest monitoring with abdominopelvic CT or magnetic resonance imaging, and chest CT, at three to six-month intervals during the first two years and annually between two to five years. In addition to cystoscopy and imaging techniques, routine blood tests and urine cytology should also be performed at regular intervals, as indicated in the NCCN guidelines (31).

Table 1. Important prospective studies related to curative radiotherapy for MIBC

Studies	Study design/ phase	Tx modality	Concomitant chemotherapy	Number of Pts	Radiotherapy	Complet response rate	Bladder preservation rate	Cancer spesific survial	Overall survival	Pelvic toxicity
Kragelj et al. (17)	Phase 2	TUR + Concurrent chemoradiotherapy	Vinblastine	84	63.8-64 Gy	78%		9 y: 51%	9 y: 25%	5y prevalance ≥ G3 Chronic: 23%
Gogna et al. (18)	Phase 2	TUR + Concurrent chemoradiotherapy	Sisplatin	113	63-64 Gy	70%		5 y: 50%		Acute: 23%
Lagrange et al. (19)	Phase 2	TUR + Concurrent chemotherapy and split course radiotherapy (45 Gy) then bx complete response: continue chemoradiotherapy (63 Gy), bx not complete response: cystectomy	Sisplatin + 5FU	51	63 Gy	66%	67%		8 y: 36%	≥ G3 Chronic: 11%
Weiss et al. (12)	Prospective	TUR +Concurrent chemoradiotherapy	Sisplatin + 5FU	112	59.4 Gy	88,40%	82%	5 y: 82%	5 y: 74%	≥ G3 Chronic: 15%
Zapatero et al. (20)	Prospective	Neoadjuvan chemotherapy + radiotherapy (P1) vs. concurrent chemoradiotherapy (P2)	Sisplatin	80	60 Gy (P1) vs. 64.8 Gy (P2)	72% vs. 80%		5 y: 82%	10 y: 60%	≥ G2 Chronic: 28%
Kaufman et al. (27)	Phase 1-2	TUR + Concurrent chemotherapy and split course radiotherapy then repeat bx ≤T1: adjuvant chemotherapy, repeat bx >T1: radical cystectomy and adjuvant chemotherapy	Cisplatin + Paclitaxel	80	Twice daily radiotherapy	81%		3 y: 83%	5 y: 56%	≥ G3 Chronic: 6% (RTOG)

Table 1. Continued

Studies	Study design/ phase	Tx modality	Concomitant chemotherapy	Number of Pts	Radiotherapy	Complet response rate	Bladder preservation rate	Cancer spesific survial	Overall survival	Pelvic toxicity
Russell et al. (46)	Phase 2	TUR + Concurrent chemotherapy and split course radiotherapy (40 Gy) then repeat bx complete response: continue chemoradiotherapy (60 Gy), bx not complete response: cystectomy	5 FU	34	60 Gy	81%			4 y: 64%	
Varveris et al. (47)	Phase 2	TUR + Concurrent chemoradiotherapy	Sisplatin + docetaxe l	42	68-74 Gy	54,70%			2 y: 78,5%	
Hussain et al. (48)	Phase 2	TUR + Concurrent chemoradiotherapy	Mitomycin + 5 FU	41	55 Gy/20 fr	71%		2 y: 68%	5 y: 36%	Acute G3: 12%
Choudhury et al. (34)	Phase 2	TUR + Concurrent chemoradiotherapy	Gemcitabine	50	52.5 Gy/20 fr	88%		3 y: 82%	5 y: 65%	Acute G3: 8%
Housset et al. (21)	Phase 3	TUR + Concurrent chemotherapy + split course radiotherapy; then bx complete response: either csytectomy or additional chemoradiotherapy, bx not complete response: cystectomy	Cisplatin + 5 FU	54	Twice daily radiotherapy - 44 Gy	74%			3 y: 59%	
Shipley et al. (22)	Phase 3	TUR + Concurrent chemotherapy + split course radiotherapy; then bx complete response: additional chemoradiotherapy, bx not complete response: cystectomy	Cisplatin	190	64-65 Gy	57%	65%		5, 10 y: 54%- 36%	
Tunio et al. (29)	Phase 3	TUR + Concurrent chemoradiotherapy (whole pelvis (WP) vs. bladder only radiotherapy (BO)	Cisplatin	230	65 Gy	93,1% (WP) - 92,8% (BO)	58.9%(WP) - 57.1(BO)		5 y: 52,9%(WP) - 51%(B0)	≥ G3 Acute: 17,6% (WP) - 13,3% (BO)
James et al. (23)	Phase 3	TUR + Concurrent Chemoradiotherapy (CRT) vs. Radioherapy (RT) and Whole Bladder Radiotherapy vs. Modified volume radiotherapy (2x2 design)	5 FU + Mitomycin C	360	64 Gy/32 fr and 55 Gy/20 fr	67% (CRT) - 65,7% (RT)			5 y: 48% (CRT) - 35% (RT)	≥ G3 Chronic: 8,3% (CRT) - 15,7% (RT) (RTOG)

MIBC: Muscle invasive bladder cancer, RTOG: Radiation Therapy Oncology Group, 5FU: 5 fluorouracil

Conclusion

Bladder cancer is categorized into two groups, NMIBC and MIBC, based on variations in treatment and prognosis. A review of studies related to definitive radiotherapy for NMIBC indicates that the existing data do not provide clear guidance on the role of radiotherapy. In contrast, the role of curative radiotherapy in MIBC has been established. Although there are no randomized controlled trials comparing curative radiotherapy to radical cystectomy, survival outcomes in appropriately selected patient groups are comparable to those observed in surgical series. The addition of concurrent chemotherapy to radiotherapy has demonstrated an improvement in response rates. For radiotherapy, either conventional fractionation accelerated hyperfractionation or hypofractionation may be chosen. The inclusion of pelvic lymph nodes remains a topic of debate. As a treatment technique, IMRT offers reduced dose for normal organs, and reduced toxicity relative to 3D-CRT.

Short Quiz

1. Which is the most commonly used agent in concomitant therapy?

A. Cisplatin

B. Carboplatin

C. Vinblastine

D. Gemcitabine

2. Which fractionation is recommended to be preferred for TMT in NCCN guideline?

A. Conventional fractionation

B. Hypofractionation

C. Accelerated hyperfractionation

D. A+B

E. A+B+C

Ethics

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.U.A., G.S.K., Concept: S.U.A., M.S., O.K., Design: S.U.A., M.S., G.S.K., O.K., Data Collection or Processing: S.U.A., M.S., O.K., Analysis or Interpretation: S.U.A., M.S., G.S.K., Literature Search: S.U.A., G.S.K., O.K., Writing: S.U.A.,O.K.

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