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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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Original Article

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Is the Bladder Cancer Patient Information Form Effective for Information?

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Abstract

Objective: The development of bladder cancer is the result of the uncontrolled proliferation of cells that line the inner surface of the bladder. Bladder cancer ranks as the seventh most commonly diagnosed cancer in males. Educating patients about bladder cancer enhances treatment adherence and fosters trust in healthcare providers. The objective of our study was to assess the efficacy and clarity of the Turkish edition of the "Bladder Cancer Patient Information Guide" developed by the European Association of Urology, Patient Information Office.

Materials and Methods: Our study was planned as a survey to raise awareness of bladder cancer, assess knowledge, and provide information about the disease. The study comprised adult patients between the ages of 18 and 79 who had been diagnosed with a primary bladder tumor and had completed at least primary school. Patients were asked about their age, gender, educational background, economic status, and the duration and history of their tobacco use. Furthermore, questions were used to collect data on the information form.

Results: Our study involved 92 patients diagnosed with primary bladder tumors. Of the patients, 80 were male and 12 were female. The mean age was 68.9±9.78. The research comprised 92 patients who were diagnosed with primary bladder tumors. It is 80 degrees Fahrenheit, with 12 hours of sunlight. The statistically significant increase in knowledge regarding the etiology, preventive measures, and characteristics of bladder tumors was observed after providing information. Furthermore, there has been a rise in awareness of the symptoms of bladder tumors and the various treatment methods available for each type.

Conclusion: The significance of informing patients about their diseases is emphasized by the research. It is crucial that the public has access to information that is both accurate and comprehensible. This is achieved through the use of brochures that have been approved by urology associations such as European Association of Urology, American Urological Association and the British Association of Urological Surgeons. Regular updates to these brochures can significantly improve the sharing of information.

Keywords: Bladder cancer, effectivity, medico-legal, patient information

Introduction

Bladder cancer arises from the unregulated proliferation of cells that line the bladder's inner surface. Bladder cancer ranks as the seventh most commonly diagnosed cancer in males. It ranks as the tenth most prevalent malignancy among both genders. The global incidence rate is 9.5 per 100,000 men and 2.4 per 100,000 women annually. Numerous studies have explored the origin and risk factors of bladder cancer. The prevalence of bladder cancer has risen during the past 60 to 70 years. This trend is particularly pronounced in less developed and developing nations, where industrialization results in carcinogenic exposure. The primary identified risk factor is smoking (1).

Educating patients about bladder cancer enhances treatment adherence and increases trust in healthcare providers. Follow-up on bladder cancer is crucial for reducing recurrence and enhancing survival rates. Educating patients on bladder cancer prevention and risk factor reduction also helps prevent medico-legal issues. Consent forms obtained during clinical evaluations or prior to surgical procedures are traditionally intended to provide information to patients. Patients also seek to access multiple information sources, including internet platforms and social media, to understand the processes associated with their diseases. Nonetheless, the accuracy and reliability of the information are essential. Various urological ass various urological associations worldwide have developed patient information forms, which have been integrated into the surgical procedure approval process for numerous centers. Grated into the surgical procedure approval process for numerous centers. These forms represent a crucial component of the information dissemination

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process to patients. Consequently, it is essential to assess the clarity and efficacy of the forms.

The objective of our study was to assess the efficacy and clarity of the Turkish edition of the" Cancer Patient Information Guide", developed by the European Association of Urology, Patient Information Office (2).

Materials and Methods

Our research was structured as a survey that provides information regarding bladder cancer and assesses the existing knowledge level. We presented the Turkish edition of the bladder cancer information leaflet from the European Urological Association Information Office to the patients (2). The enhancement in knowledge was assessed using a questionnaire administered prior to, and following, the reading. Additionally, we evaluated the "Turkish Readability Index" from the Turkish version of the information leaflet. The index created by Ateşman (3), utilizing the "Flesch Reading Ease" formula, served as the Turkish Readability Index. The text's word and sentence lengths determine the index. The computation excluded headings, references, and abbreviations in the data form. The grading ranges from 0 to 100, with higher scores correlating to enhanced readability and comprehension.

The study included adult patients with primary bladder tumors, aged 18 to 79 years, who had at least a primary education. We set our sample size estimation with a significance level of 0.05 and power of 0.2. The effect size was deemed acceptable at 0.3. We used the "One Sample Case" statistical approach for the t-test and mean calculations. The sample size was established at 71 by G*Power analysis. In light of the potential danger of patients incorrectly completing the questionnaires, the sample size was established at 80 to account for possible patient loss; a total of 92 patients were included in our study.

We conducted the assessment using questionnaire items derived from the subjects outlined in the bladder cancer information document. We questioned the patients about their age, gender, level of education, financial status, and history and duration of their tobacco consumption. We also administered questionnaire items to assess the data related to the information form. Ethics committee approval, numbered AEŞH-EK1-2023-786, was secured on 20 December 2023 from University of Health Sciences Türkiye, Ankara Etlik City Hospital.

Statistical Anaysis

All phases of the study adhered to the principles of the Declaration of Helsinki. Parametric tests (paired sample t-test, Pearson correlation test) and non-parametric tests (Wilcoxon test, Spearman correlation, McNemar test, Kappa test, and chi-square test) were utilized to analyze the data. Statistical analysis was conducted using SPSS software (version 20, SPSS Inc., Chicago, USA).

Results

Our study involved 92 patients diagnosed with primary bladder tumors. Of the patients, 80 were male and 12 were female. The mean age was 68.9±9.78 (Table 1). The predominant diagnosed age range was 50-60 years (n=41, 46.6%) (Figure 1). The Tables 2-4 display the survey questions, responses, and statistical outcomes.

We determined the Turkish Readability Index to be 53.3. The average sentence length is 11.9 words, while the average word length is 2.85 characters. The index score indicates a readability level of 11th to 12th grade. The information guide is challenging to comprehend, possibly because patients with only primary education represent the largest demographic group.

Following the survey, we examined the changes in patient' knowledge regarding various aspects of bladder cancer. Table 5 displays the associated modifications and outcomes of the statistical analysis.

It's interesting that after reading the informational guide, the number of patients who chose "total removal of the bladder" as their treatment for non-muscle-invasive bladder cancer rose from 27 to 35. The increase was statistically significant (p=0.024). We must provide patients with a comprehensive understanding regarding the management of non-muscle invasive bladder cancer.

The survey asked participants about the usefulness of the information guide. Thirty-six patients responded that it was somewhat useful, thirty-four patients indicated it was fairly useful, twelve patients thought it was very useful, and four patients considered it extremely useful. The average score was determined to be 2.69±0.97 (Figure 2).

Discussion

Patients must be informed of their medical conditions and the surgical procedures to be undertaken. It is essential to elucidate the rationale for the surgery, treatment alternatives, benefits, and risks to ensure the validity of the informed consent. Patients explore various sources for information regarding their medical problems. It is essential that patients receive accurate guidance in this matter. The British Association of Urological Surgeons (BAUS) and the Patient Information Office of the European Urological Association provide informational resources

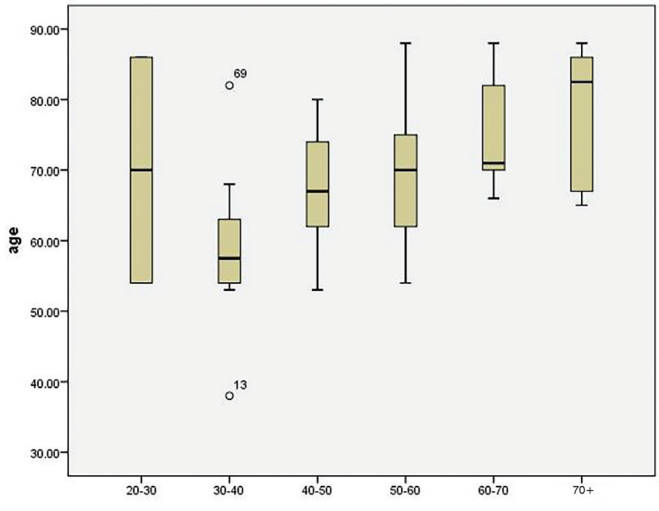

Figure 1. Age range at diagnosis of bladder tumour

Table 1. Demographic datas and tobacco using status data			
Parameters	**Sub parameters**	**Number (n)**	**Ratio (%)**
Gender	Female	12	13.04
	Male	80	86.96
Year	Min	38	
	Max	88	
	Mean	68.9	
Marital status	Maried	83	90.22
	Single	9	9.78
Education	Primary	42	45.7
	High school	34	37
	University	15	16.3
	Master degree	1	1.1
Economic status	Poor <17 kŁ	20	21.7
	Middle 17 k-35 kŁ	47	51.1
	Good 35 k-70 k	21	22.8
	Very good <70 k	4	4.3
Tobacco products using	Using	76	82.6
	Not using	16	17.4
Tobacco products using	10-20 (year)	27	29.3
Time	20-30 (year)	39	42.4
	30-40 (year)	17	18.5
	>40 years	9	9.8
I wish I hadn't used it	Yes	74	80.4
	No	18	19.6

on bladder cancer. Patients may be provided with these and comparable guidelines established by scientific associations. The dependability and clarity of the information in these standards are ethically and legally significant. Consequently, it is essential to assess the clarity of these guidelines and their efficacy for patients (4).

Graham et al. (5) assessed the comprehensibility of informed consent documents. Their article included certain criteria for assessment. The "Flesch Reading Ease" assessment assigns a score ranging from 0 to 100 points to a text. A score exceeding 60 signifies a reading proficiency equivalent to the 8th grade level. This level indicates that readability and comprehensibility is appropriate for adults. Likewise, the "Flesch-Kincaid Grade Level" is a readability metric designed to assess the complexity of the words and sentences within a document. The score ranges from 0 to 18. Another assessment criterion is the Simple Measure of Gobbledygook (SMOG) score. The SMOG score assesses the years of education requisite for an individual to comprehend a text (5). SMOG is recognized as a readability scale that offers a precise assessment. Graham et al. (5) assert that the SMOG scale demonstrates a more consistent and robust connection compared to the Flesch-Kincaid in validation trials. It is particularly favored in the health literature. The prevalence of polysyllabic terms in health literature diminishes text comprehension. Consequently, it has been asserted that using straightforward language is essential for patient information pamphlets. They asserted that the information pamphlets produced by BAUS were challenging to comprehend and necessitated a higher reading level than SMOG indicates. This circumstance precludes the use of leaflets as the sole source of information for the United Kingdom. It was underscored that the information must be articulated succinctly and clearly in collaboration with lay patient groups. The Turkish Readability Index of the information guide in our investigation was 53.3. This index score corresponds to a readability level of 11th to 12th grade. The majority of survey

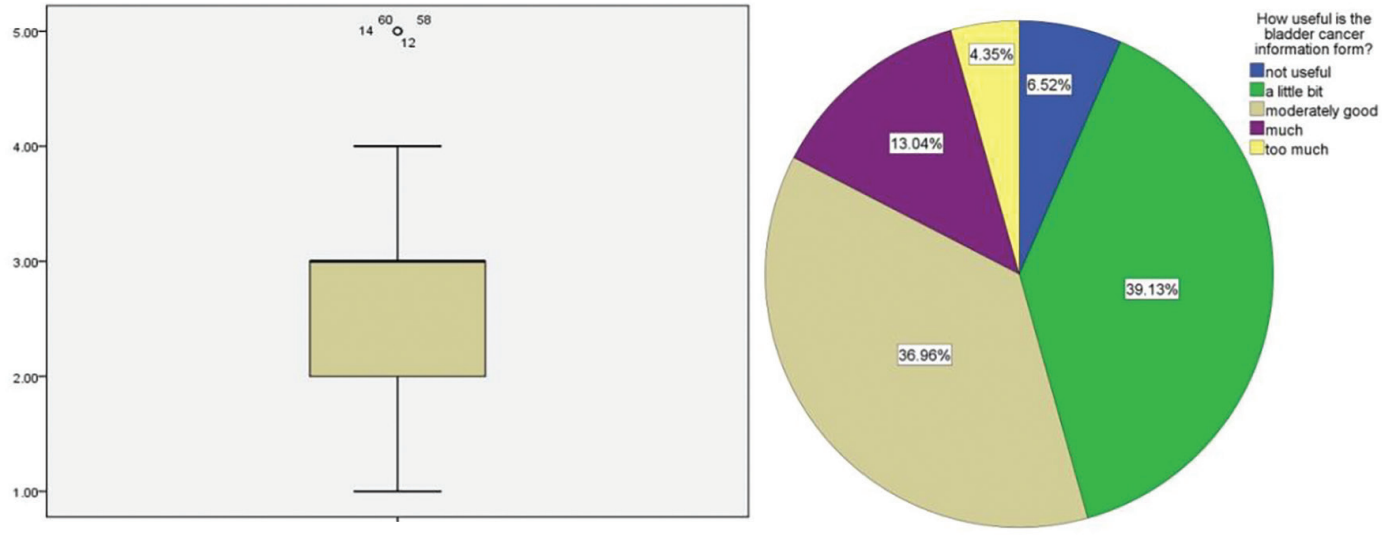

Figure 2. How useful is the bladder cancer information form?

Table 2. Answers to the survey questions and statistical results			
What is a bladder tumour?	**Before giving information (n-%)**	**After giving information (n-%)**	**p<0.05**
Abnormal enlargement of the bladder	5 (5.4%)	10 (10.9%)	
Ballooning in the bladder	29 (31.5%)	14 (15.2%)	**0.011**
It is the growth of abnormal tissue (tumour) in the bladder.	**58 (63%)**	**68 (73.8%)**	
What are the etiological factors (causes) of the bladder)	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Consumption of tobacco products (cigarettes, etc.) paint and petrol products, urinary tract infections	**4 (4.3%)**	**8 (8.7%)**	
Chronic alcohol consumption	66 (71.7%)	78 (84.8%)	**0.020**
Working in health facilities and security areas (radiation exposure)	6 (6.5%)	16 (17.4%)	
Chronic diseases	4 (4.3%)	2 (2.2%)	
Which option is correct about the staging of bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Extending to muscle tissue, not extending to muscle tissue, advanced, metastatic	**6 (6.5%)**	**24 (26.1%)**	
Extending to the liver, extending to the lung, extending to the prostate	42 (45.7%)	32 (34.8%)	**0.003**
Growing into the bladder, extending outside the bladder	42 (45.7%)	34 (37%)	
Superficial, deep, extending to distant organs	2 (2.2%)	2 (2.2%)	
What should we do to prevent bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Do not consume tobacco products, drink plenty of water, avoid harmful chemicals	**50 (54.3%)**	**65 (70.7%)**	
Avoiding alcohol, supertive lifestyle	22 (23.9%)	22 (23.9%)	**0.006**
Protein-rich diet	16 (17.4%)	4 (4.3%)	
Reguler kidnet stone passing	4 (4.3%)	1 (1.1%)	

Table 3. Answers to the survey questions and statistical results-2			
What are the symptoms of bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	**p<0.05**
Red coloured urine, painful micturition	20 (21.7%)	12 (13%)	
Painless, red, haemorrhagic urination, abdominal pain, frequent urination	**54 (58.7%)**	**70 (76.1%)**	**0.036**
Frequent urination at night	16 (17.4%)	8 (8.7%)	
Frequent urinary tract infections	2 (2.2%)	2 (2.2%)	
Which tests are required for the diagnosis of bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Blood, urinalysis and ECO	6 (6.5%)	10 (10.9%)	
Holter test	66 (71.7%)	4 (4.3%)	0.163
Voiding test	6 (6.5%)	13 (14.1%)	
Urinalysis, ultrasonography, cystoscopy, CT and/or MRI	**59 (64.1%)**	**65 (70.7%)**	
What is non-muscle invasive bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Covers the superficial layers of the bladder	21 (22.8%)	24 (26.1%)	
Cancer that grows into the bladder	43 (46.7%)	29 (31.5%)	
Not extented into the deeper layers of the bladder wall	**24 (26.1%)**	**40 (43.5%)**	
Tumour extending outside of the bladder	1 (1.1%)	2 (2.2%)	0.081
What is the treatment of non-muscle invasive bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Transurethral resection of bladder tumour and intra-vesical irrigation of the bladder	**33 (35.9%)**	**31 (33.7%)**	
Complete removal of the bladder	27 (29.3%)	35 (38%)	**0.024**
Intra-vesical chemotheraphy	26 (28.3%)	22 (23.9%)	
Radiotheraphy (radiation) of the bladder	6 (6.5%)	4 (4.3%)	
CT: Computed tomography, MRI: Magnetic resonance imaging, ECO: Echcardiography			

Table 4. Answers to the survey questions and statistical results-3			
Which is the correct option for the treatment of muscle invasive bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	**p<0.05**
Complete removal of the bladder, bladder-sparing surgery, CT, RT	**20 (21.7%)**	46 (50%)	**0.001**
Endourological resection of bladder tumour (through the urethra)	61 (66.3%)	38 (41.3%)	
Complete removal of the prostate	9 (9.8%)	6 (6.5%)	
Complete removal of the urinary tract	2 (2.2%)	2 (2.2%)	
Which is correct about the preventive treatment of bladder cancer?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Complete removal of the bladder	5 (5.4%)	6 (6.5%)	0.060
TUR-MT and RT are used to locally treat or control a bladder tumour	**44 (47.8%)**	**53 (57.6%)**	
Intra-vesical chemotheraphy	31 (33.7%)	29 (31.5%)	
Complete removal of the cancerous area in the bladder	12 (13%)	4 (4.3%)	
What is a positive surgical margin?	**Before giving information (n-%)**	**After giving information (n-%)**	p<0.05
Cancer is the presence of cancer cells in a circle of normal tissue around the cacer	**38 (41.3%)**	**45 (48.9%)**	0.330
The presence of a secondary cancer cell group within the cancer cells	36 (39.1%)	34 (37%)	
During the treatment of bladder cancer, it is a different cancer againg	16 (17.4%)	12 (13%)	
Kidney tumour is observed simultaneously with bladder cancer	2 (2.2%)	1 (1.1%)	
CT: Computed tomography, RT: Radiotheraphy, TUR-MT: Maximal transurethral bladder tumor resection			

participants possessed a primary education. We believe that the guideline is challenging to comprehend. It is essential to assess the guideline for its simplification and enhancement of comprehensibility.

No other study in the literature assesses the efficacy of the information guide, using exam questions similar to those in our study. Askari and Shergill (6) evaluated the sufficiency of brochures on extracorporeal shock wave lithotripsy. They collected data from 12 distinct centers and assessed the brochures to determine what issues should be incorporated. Although none of the brochures included details regarding the procedure's location, the majority included information on pre-procedural preparation, analgesia, and follow-up care. Complications, including infection, hematuria, calculi, and renal atrophy and injury, were presented in the brochures with differing frequency. No brochure indicated the possibility of urinary retention or visceral damage. Diagrams of anatomy and procedures were included in fewer than fifty percent of the brochures (6). This study has not assessed numerous brochures. Our study assessed the European Society of Urology's Bladder Cancer Information brochure by employing a knowledge level measurement approach based on questions developed around the outlined topics.

Study Limitations

The main limitation of our study is that the participants predominantly have attained primary school educational levels. The Turkish edition of this informational guide, produced by the Patient Information Office of the European Association of Urology, is challenging to comprehend. Therefore, had the guide comprehended by the patients been more intelligible, it would have influenced the outcomes of our research. This limitation reveals the purpose of our study.

Conclusion

It is crucial to confirm that the informed consent forms that patients are provided with prior to treatment are valid and contain adequate information. The adequacy of the information documents provided to patients was assessed in the context of their comprehension levels in our study. For instance, it was noted that the correct response rates increased following the provision of information regarding bladder cancer, its etiological factors, staging, prevention, and treatments. It has been verified that these increases are also statistically significant. Brochures that have been approved by urology associations such as EAU, AUA, and BAUS are essential for the general public to access accurate and comprehensible information. The dissemination of information will be significantly enhanced through the consistent updating of these brochures.

Ethics

Ethics Committee Approval: All phases of the study adhered to the principles of the Declaration of Helsinki. Ethics committee approval, numbered AEŞH-EK1-2023-786, was secured on 20 December 2023 from University of Health Sciences Türkiye, Ankara Etlik City Hospital.

Informed Consent: Informed consent forms were obtained from all volunteers.

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Contribution: There is not any contributors who may not be listed as authors.

Table 5. Changes in knowledge level about bladder cancer				
Levels of knowledge	**Increase (n)**	**Decrease (n)**	**Unchanged (n)**	**p<0.05**
Formation and stages of bladder cancer	50	16	26	**0.001**
Diagnostic methods of bladder tumour	30	32	30	0.985
Treatment options of bladder cancer	34	23	35	0.134
Metastatic bladder cancer	40	6	46	**0.001**
Recurrent bladder cancer	38	9	45	**0.001**
Bladder cancer follow-up	33	13	46	**0.002**
Level of anxiety about bladder cancer surgery	35	27	30	0.383
Prevention of bladder cancer	31	22	39	0.142
Benefit of smoking cessation advice for bladder cancer	32	11	49	**0.014**

Footnotes

Authorship Contributions

Concept: F.S., F.Ç., Design: F.S., F.Ç., Data Collection or Processing: F.S., S.K., D.D., Analysis or Interpretation: F.S., M.A., D.D., M.A.İ., Literature Search: S.K., M.A., Writing: F.S., M.A., M.A.İ.

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Original Article

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ChatGPT-3.5 and ChatGPT-4 Performance in Testicular Cancer: A Comparative Study

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Abstract

Objective: The aim of our study is to assess the reliability of Chat Generative Pre-trained Transformer (ChatGPT), compare the performance of ChatGPT-4 to ChatGPT-3.5, and explore its potential roles in healthcare decision-making.
Materials and Methods: Thirty questions related to testicular cancer were prepared, based on the 2023 European Association of Urology guidelines and clinical experience. These questions were systematically posed to ChatGPT-3.5 and ChatGPT-4, and responses were rated by three independent urologists using a six-point Likert scale. The median score from the three specialists was used as the final score.
Results: Both ChatGPT versions provided an incorrect answer to one question, scoring a one. For GPT-3.5 and GPT-4, the percentage of responses considered incorrect by the urologists was 20% and 13.3%, respectively, while correct responses (scoring 3 or higher) accounted for 80% and 86.7%. For general information-diagnosis questions, GPT-3.5 and GPT-4, had average scores of 4.29 and 4.80, with median values of 4.27 and 4.67. For treatment follow-up questions, average scores were 3.60 and 4.16, with median values of 3.60 and 4.20. GPT 4 generally outperformed GPT-3.5, but the difference was not statistically significant ($p>0.05$).
Conclusion: Our study shows that ChatGPT-4 is more reliable and accurate than ChatGPT-3.5 in testicular cancer-related queries. Continued development of its database and clinical capabilities could optimize ChatGPT's utility in healthcare.
Keywords: Artificial intelligence, ChatGPT, natural language processing, testicular cancer

Introduction

To improve the survival rates of cancer patients, rapid diagnosis and optimal treatments are essential. These patients seek various sources of information to address their health concerns but are often exposed to misinformation on platforms such as Google and YouTube (1). In this context, natural language processing (NLP) models have the potential to enhance patients' access to accurate medical information. Large language models (LLMs) should be evaluated for their accuracy in providing medical information. Artificial intelligence (AI) programs have demonstrated diagnostic accuracy comparable to that of medical professionals and have even outperformed physicians in delivering high-quality, empathetic responses to patient inquiries (2,3).

One of the LLMs, the Chat Generative Pre-trained Transformer (ChatGPT), is an NLP tool capable of understanding and generating human-like text (4). Developed by OpenAI, ChatGPT was launched in November 2022 and has been widely used by millions of users for information retrieval and task completion. ChatGPT-4, an advanced version provided by OpenAI, offers improvements over its predecessor, ChatGPT-3.5. This model is reported to have enhanced reasoning capabilities and a significantly larger knowledge base, enabling it to solve complex problems with greater accuracy (5). Trained on extensive datasets, ChatGPT possesses the ability to generate human-like text rapidly. Its rapid adoption highlights its accessibility and ease of use (6). In the medical field, it holds the potential to assist healthcare professionals in various aspects, including patient education, diagnosis, and treatment planning (7).

ChatGPT's success in the United States Medical Licensing Examination (USMLE) suggests that AI has the potential to revolutionize medicine (8). ChatGPT-4 is anticipated to enhance

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clinical accuracy and reduce error rates. While ChatGPT-3.5 achieved a 60% success rate in the USMLE, ChatGPT-4 significantly improved this performance, reaching 87% (9,10). At the time of our study, ChatGPT-3.5 was available for free, while ChatGPT-4 was accessible through a subscription model, with claims of improved accuracy and speed (11).

In this study, we aimed to compare the reliability of responses provided by ChatGPT-3.5 and ChatGPT-4 to urology related questions based on the strong recommendations and clinical expertise outlined in the 2023 European Association of Urology (EAU) guidelines on testicular cancer. Our objective was to assess the practicality of AI in healthcare, particularly for users with limited resources. This study is expected to provide valuable insights into the benefits and limitations of AI models in clinical education and medical decision-making.

Materials And Methods

In our study, a total of 30 questions at three different levels of difficulty-basic, intermediate, and advanced-were prepared by three expert urologists: Ümit Uysal (ÜU), Süleyman Sağır (SS), Murat Uçar (MU), each with a minimum of four years of clinical experience. The questions were developed using high-grade recommendations from the testicular cancer section of the 2023 EAU guidelines as well as clinical expertise. Two of the urologists ÜU, MU are certified as Fellows of the European Board of Urology. Only questions written in English were included in the study. This rigorous question development and evaluation process was carefully conducted to enhance the reliability of the responses. In the development of the questions, clinical practice-oriented scenarios, up-to-date information from the literature, and expert opinions were taken into account. Furthermore, the questions were reviewed and validated by an expert panel of three urologists ÜU, SS, MU in terms of their relevance to clinical practice, adherence to current guidelines, and overall validity. This structured approach was designed to enhance the reproducibility and reliability of the study. On April 3, 2024, all questions were systematically submitted to both ChatGPT-3.5 and ChatGPT-4. Subsequently, each response was independently evaluated by three urology specialists ÜU, SS, MU based on the 2023 EAU guidelines and their own clinical experience. More specifically, the accuracy of the responses was rated using a six-point Likert scale: 1 indicating completely incorrect; 2 indicating more incorrect than correct; 3 indicating equally incorrect and correct; 4 indicating more correct than incorrect; 5 indicating almost correct; and 6 indicating completely correct (12). To enhance the reliability of the evaluations made by the experts, each response was independently scored, and the final score was determined by calculating the median. Although consensus-based approaches such as the Delphi method were not used in our study, the potential of such methods to improve inter-rater consistency can be investigated in future research. This study did not involve any human subjects or health data; therefore, ethical approval and patient informed consent were not required.

Statistical Analysis

Data analysis was performed using SPSS 24.0 software package (SPSS Inc., Chicago, IL). Descriptive statistics were calculated. Differences in scores between the two ChatGPT models, and the differences for each question group, were evaluated using the Wilcoxon test.

Results

In Table 1, the question "When should cranial imaging be performed in testicular cancer?" had the same average score for ChatGPT-3.5 and ChatGPT-4, both receiving 6.00 points. Both models received equal scores. In contrast, for the question "What is the most appropriate treatment for a patient with germ cell neoplasia in situ in a solitary testis?", both models scored 1.00, indicating that both models, including ChatGPT provided completely incorrect answers.

In our study, 20% of responses from ChatGPT-3.5 were evaluated as incorrect by specialists, while 80% of responses, scoring 3 or higher, were considered correct. This result indicates that the majority of responses from ChatGPT-3.5 were deemed correct. For ChatGPT-4, the percentage of incorrect responses was lower at 13.3%, and the percentage of correct responses was higher at 86.7%. This demonstrates that ChatGPT-4's responses were more accurate and reliable than those of GPT-3.5. While both models exhibited high accuracy, ChatGPT-4 provided fewer incorrect and more accurate responses according to the specialist physicians.

As shown in Table 2, for ChatGPT-4, 20.0% of the responses in the general information-diagnosis category received 5 points, and 13.3% received 6 points. The proportion of responses receiving low scores was quite small, with only 3.3% receiving 2 points. This indicates that ChatGPT-4 provided responses at a higher level of accuracy in this category. In the treatment-follow-up category, 13.3% of the responses received 5 or 6 points, while 6.7% received 2, 3, and 4 points. These results show that ChatGPT-4 also achieved high accuracy in this category, with responses generally receiving higher scores.

ChatGPT-4 provided more accurate and reliable responses than ChatGPT-3.5, with higher scores in both the general information-diagnosis and treatment-follow-up categories. ChatGPT-3.5 received moderately high scores in the general information-diagnosis category compared to its wider distribution of scores in the treatment-follow-up category. This demonstrates that ChatGPT-4 performed better .

When examining the responses of ChatGPT-3.5 and ChatGPT-4, that were evaluated as correct and incorrect by specialist physicians in the general information-diagnosis and treatment-follow-up subcategories, 43.3% of the responses in the general information-diagnosis category for ChatGPT-3.5 were evaluated as correct, while 6.7% were considered incorrect. This shows that ChatGPT-3.5 had a high rate of correct answers in this category, although some responses were evaluated as incorrect. In the treatment-follow-up category, 36.7% of the responses were evaluated as correct, while 13.3% were evaluated as incorrect. Although ChatGPT-3.5 generally tended to provide correct answers in this category, the rate of incorrect answers was higher compared to the general information-diagnosis category.

For ChatGPT-4, the correct response rate in the general information-diagnosis category was quite high at 46.7%, while

Table 1. Descriptive statistics of the evaluation scores of three expert physicians for ChatGPT-3.5 and ChatGPT-4's responses										
	ChatGPT-3.5					ChatGPT-4				
	Min.	Max.	X	SS	Median	Min.	Max.	X	SS	Median
General information-diagnosis questions										
What should a physician do first when a male patient presents to the urology clinic with suspected testicular cancer?	4.00	4.00	4.00	0.00	4.00	4.00	5.00	4.33	0.58	4.00
Which recurring genetic marker is associated with invasive GHNIS*?	4.00	4.00	4.00	0.00	4.00	6.00	6.00	6.00	0.00	6.00
What are the epidemiological risk factors for testicular cancer?	3.00	4.00	3.67	0.58	4.00	5.00	6.00	5.33	0.58	5.00
Which serum tumor marker might increase in a patient with a pathology report of "pure seminoma"?	4.00	5.00	4.33	0.58	4.00	5.00	6.00	5.67	0.58	6.00
In a male patient with "gynecomastia" detected during physical examination, which types of testicular cancer should be considered?	2.00	3.00	2.33	0.58	2.00	3.00	4.00	3.33	0.58	3.00
Is the sensitivity and specificity of micro RNA high in diagnosing and monitoring testicular cancer?	4.00	5.00	4.33	0.58	4.00	5.00	6.00	5.67	0.58	6.00
When should scrotal MRI be performed in a patient suspected of having testicular cancer?	3.00	3.00	3.00	0.00	3.00	3.00	4.00	3.33	0.58	3.00
Is the sensitivity and specificity of CT high in detecting lymph node metastasis in testicular cancer?	4.00	4.00	4.00	0.00	4.00	4.00	5.00	4.67	0.58	5.00
Is there a role for FDG PET-CT in testicular cancer?	4.00	4.00	4.00	0.00	4.00	5.00	6.00	5.33	0.58	5.00
When should cranial imaging be performed in testicular cancer?	6.00	6.00	6.00	0.00	6.00	6.00	6.00	6.00	0.00	6.00
Is there a role for bone scanning in staging testicular cancer?	2.00	3.00	2.33	0.58	2.00	2.00	3.00	2.33	0.58	2.00
What should be done for a male patient with a retroperitoneal mass normal hCG and AFP levels, and no palpable testicular mass?	6.00	6.00	6.00	0.00	6.00	5.00	5.00	5.00	0.00	5.00
Is routine contralateral biopsy performed in testicular cancer?	4.00	5.00	4.67	0.58	5.00	4.00	5.00	4.33	0.58	4.00
What should be done to preserve fertility in a male patient diagnosed with testicular cancer?	6.00	6.00	6.00	0.00	6.00	5.00	6.00	5.33	0.58	5.00
What should be considered if serum tumor markers remain elevated after an orchiectomy performed for suspected testicular cancer?	5.00	6.00	5.67	0.58	6.00	5.00	6.00	5.33	0.58	5.00
Treatment-follow-up questions										
16. Is there a role for testis-sparing surgery in testicular cancer?	2.00	2.00	2.00	0.00	2.00	3.00	3.00	3.00	0.00	3.00
17. Why is scrotal orchiectomy not recommended in the surgical treatment of testicular cancer?	4.00	5.00	4.67	0.58	5.00	6.00	6.00	6.00	0.00	6.00
18. What is the most appropriate treatment for a patient diagnosed with GHNIS in a solitary testis?	**1.00**	**1.00**	**1.00**	**0.00**	**1.00**	**1.00**	**1.00**	**1.00**	**0.00**	**1.00**

Table 1. Continued

	ChatGPT-3.5					ChatGPT-4				
	Min.	Max.	X	SS	Median	Min.	Max.	X	SS	Median
19. Is adjuvant radiotherapy routinely performed for stage 1 seminomas?	5.00	6.00	5.33	0.58	5.00	5.00	5.00	5.00	0.00	5.00
20. What should be the next treatment plan if tumor size is 5 cm and rete testis invasion is present in a patient with stage 1 seminoma?	2.00	3.00	2.67	0.58	3.00	3.00	4.00	3.33	0.58	3.00
21. What is the treatment option for a high-risk clinical stage 1 non-seminoma patient with vascular invasion?	4.00	4.00	4.00	0.00	4.00	5.00	5.00	5.00	0.00	5.00
22. Should we immediately perform orchiectomy in a life-threatening situation with widespread metastases in a patient with a testicular mass?	6.00	6.00	6.00	0.00	6.00	5.00	5.00	5.00	0.00	5.00
23. If a patient who underwent orchiectomy for suspected testicular cancer is diagnosed with stage 1 seminoma and refuses adjuvant chemotherapy and radiotherapy, what should be recommended?	5.00	6.00	5.67	0.58	6.00	6.00	6.00	6.00	0.00	6.00
24. What is the recommended minimum follow-up schedule for clinical stage I seminoma after active surveillance or adjuvant treatment (chemotherapy or radiotherapy)?	3.00	3.00	3.00	0.00	3.00	4.00	4.00	4.00	0.00	4.00
25. Should a testicular prosthesis be recommended to all patients who undergo orchiectomy for testicular cancer?	2.00	2.00	2.00	0.00	2.00	2.00	2.00	2.00	0.00	2.00
26. What should be the next treatment step if recurrence occurs after nerve-sparing RPLND in clinical stage 1 non-seminoma?	4.00	4.00	4.00	0.00	4.00	5.00	6.00	5.67	0.58	6.00
27. What is the alternative treatment to chemotherapy for a patient with clinical stage 2b seminoma?	2.00	2.00	2.00	0.00	2.00	2.00	2.00	2.00	0.00	2.00
28. What chemotherapy protocol should be applied if bleomycin cannot be administered in a patient with advanced metastatic non-seminomatous testicular cancer?	4.00	4.00	4.00	0.00	4.00	5.00	6.00	5.67	0.58	6.00
29. How should thromboprophylaxis be performed to prevent thromboembolic events in a young male patient receiving chemotherapy for testicular cancer?	3.00	4.00	3.33	0.58	3.00	4.00	4.00	4.00	0.00	4.00
30. What is the minimum duration of contraception recommended after completing treatment for testicular cancer?	4.00	5.00	4.33	0.58	4.00	4.00	5.00	4.67	0.58	5.00

*Germ cell neoplasia in situ, ChatGPT: Chat Generative Pre-trained Transformer, Min.: Minimum, Max.: Maximum, SS: Standard score, RNA: Ribonucleic acid, MRI: Magnetic resonance imaging, FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, hCG: Human chorionic gonadotropin, AFP: Alpha-fetoprotein, RLND: Retroperitoneal lymph node dissection

the incorrect response rate remained low at 3.3%. This indicates that ChatGPT-4 performed very well in this category and largely provided correct responses. In the treatment-follow-up category, the correct response rate was 40%, while the incorrect response rate was 10.0%. This shows that ChatGPT-4 was generally successful in this category as well, although there were a few incorrect responses. ChatGPT-4 had higher accuracy rates than ChatGPT-3.5 in both the general information-diagnosis and treatment-follow-up categories. In the general information-diagnosis category, ChatGPT-4 provided more accurate responses with fewer errors compared to ChatGPT-3.5. Although ChatGPT-4 was more successful in the treatment-follow-up category than ChatGPT-3.5, both systems demonstrated similar accuracy rates. These results indicate that ChatGPT-4 generally provided more reliable and accurate responses, compared to ChatGPT-3.5.

As shown in Table 3, the average score for the ChatGPT-3.5 model in general information-diagnosis questions was 4.29, with a median of 4.27, while the average score for the ChatGPT-4 model was 4.80, with a median of 4.67. According to the results

of the Wilcoxon test, the z-value was -1.633 and the p-value was 0.102, indicating that there was no statistically significant difference between the two models. For the treatment-follow-up questions, the average score for the ChatGPT-3.5 model was 3.60, with a median of 3.60, while the average score for the ChatGPT-4 model was 4.16, with a median of 4.20. According to the Wilcoxon test results, the z-value was -1.633 and the p-value was 0.102, again, showing no statistically significant difference between the two models. The results of the Wilcoxon test indicated that there was no statistically significant difference between the ChatGPT-3.5 and ChatGPT-4 models for both general information and diagnosis and treatment and follow-up questions (p>0.05). However, it was observed that the ChatGPT-4 model had higher average scores in both categories. This suggests that ChatGPT-4 generally performed better than ChatGPT-3.5, although the difference was not statistically significant.

Table 2. Score distribution of ChatGPT-3.5 and ChatGPT-4 responses based on subcategories (general information-diagnosis and treatment-follow-up)

		Score	n	%
ChatGPT-3.5	**General information-diagnosis**	2	2	6.7
		3	1	3.3
		4	7	23.3
		5	1	3.3
		6	4	13.3
	Treatment-follow-up	1	1	3.3
		2	3	10.0
		3	3	10.0
		4	4	13.3
		5	2	6.7
		6	2	6.7
ChatGPT-4	**General information-diagnosis**	2	1	3.3
		3	2	6.7
		4	2	6.7
		5	6	20.0
		6	4	13.3
	Treatment-follow-up	1	1	3.3
		2	2	6.7
		3	2	6.7
		4	2	6.7
		5	4	13.3
		6	4	13.3

ChatGPT: Chat Generative Pretrained Transformer

Discussion

In recent years, advancements in NLP technologies and deep learning hardware have led to significant progress in the field of LLMs. ChatGPT, a state-of-the-art LLM built upon ChatGPT-3.5 and GPT-4, demonstrates exceptional capabilities in general language comprehension and reasoning (13). The AI chatbot ChatGPT has shown promising performance across various domains, including medical science, business, and law. However, its accuracy in handling medical queries requiring domain-specific expertise, particularly in the field of urology, remains uncertain. The purpose of this study was to assess the ability and performance of ChatGPT in responding to 30 questions, prepared based on high-level recommendations from the testicular cancer section of the 2023 EAU guidelines, as well as clinical experience. Furthermore, we aimed to determine whether there is a significant performance difference between ChatGPT-3.5 and ChatGPT-4, with the goal of clarifying their potential roles in healthcare decision-making processes.

Various studies have demonstrated that GPT-4 generally achieves a higher accuracy rate compared to GPT-3.5. In a study comparing the performance of ChatGPT-3.5 and GPT-4 on standard urology multiple-choice questions, a total of 700 questions were presented to both models, and the results were analyzed. GPT-4 exhibited a higher accuracy rate than GPT-3.5 (44.4% vs. 30.9%). Notably, GPT-4 was found to be more successful in areas such as urologic oncology, sexual medicine, and pediatric urology (14). Similarly, in another study comparing the performance of ChatGPT-3.5 and ChatGPT-4 in European Board of Urology examinations, ChatGPT-4 demonstrated significantly better accuracy across all exams compared to ChatGPT-3.5 (15). Tsai et al. (16) demonstrated in their study that ChatGPT-4 outperformed ChatGPT-3.5 in terms of quality,

Table 3. A statistical comparison of the responses provided by ChatGPT-3.5 and ChatGPT-4 models to general information-diagnosis, treatment-follow-up questions

Min.		Evaluation of ChatGPT-3.5					Evaluation of ChatGPT-4					Wilcoxon	
		Max.	X	SD	Median	Min	Max.	X	SD	Median	Z	p-value	
General information-diagnosis		4.07	4.53	4.29	0.23	4.27	4.47	5.27	4.80	0.42	4.67	-1.633	0.102
Treatment-follow-up		3.40	3.80	3.60	0.20	3.60	4.00	4.27	4.16	0.14	4.20	-1.633	0.102
Wilcoxon test	Z	-1.633					-1.633						
	p-value	0.102					0.102						

ChatGPT: Chat Generative Pretrained Transformer, Min.: Minimum, Max.: Maximum, SD: Standard deviation

adherence to clinical guidelines, and alignment with expert opinions when providing cancer treatment recommendations. Another study comparing the diagnostic capabilities of GPT-3.5 and GPT-4.0 in surgery revealed that GPT-4.0 exhibited higher accuracy for both primary and secondary diagnoses, indicating significant diagnostic potential (17). In a study examining the performance of GPT-4 in orthopedic surgery board questions, GPT-4 accurately answered 63.4% of the questions, while GPT-3.5 correctly answered only 46.3%. GPT-4 demonstrated significantly better performance on orthopedic board-style questions (18). Another study assessing the accuracy of ChatGPT references in the disciplines of head and neck surgery and otolaryngology showed that ChatGPT-4.0 performed better in terms of reliability compared to version 3.5 (19).

Other studies in the field of urology have also demonstrated the superior performance of GPT-4. For instance, in a comparative analysis of advanced AI strategies in renal oncology, another study compared GPT-3.5 and GPT-4.0. The average accuracy rates of responses to 30 questions related to renal cell carcinoma, prepared by urology specialists, were 67.08% for ChatGPT-3.5 and 77.50% for ChatGPT-4.0. ChatGPT-4.0 outperformed ChatGPT-3.5 with a significantly higher accuracy rate (20). In another study evaluating the performance of ChatGPT-4 in answering questions related to urolithiasis, it was found that ChatGPT accurately and satisfactorily responded to more than 95% of the urolithiasis-related questions (21). Furthermore, a study investigating ChatGPT's performance in the diagnosis and treatment of urological trauma concluded that ChatGPT demonstrated a highly competent and reliable performance in managing urological trauma cases (22).

On the other hand, a study examining the quality of ChatGPT-4.0's responses to frequently asked popular questions about prostate, bladder, kidney, and testicular cancers, as well as questions selected from the 2023 EAU Oncology guidelines, revealed mixed findings. While ChatGPT demonstrated commendable accuracy rates when answering popular questions related to urologic cancers, its performance in providing responses consistent with EAU guideline-based questions was found to be unsatisfactory (23). Similarly, another study assessing ChatGPT-4's responses to 195 clinical questions related to prostate cancer, prepared with consideration of the EAU 2023 guidelines, demonstrated that ChatGPT exhibited poor accuracy (24). Furthermore, a study evaluating ChatGPT's performance on standard multiple-choice urology examinations also reported suboptimal performance (14). In our study, we observed that the responses provided by ChatGPT-3.5 to the questions related to testicular cancer, mostly received moderate scores (4 points), whereas the responses from ChatGPT-4 received higher scores (5 and 6 points). This finding suggests that GPT-4 provided more accurate or satisfactory answers as evaluated by expert clinicians. The assessment of GPT-4 revealed that the incorrect response rate was 13.3%, which was lower than that of GPT-3.5. Meanwhile, the correct response rate was higher for GPT-4, reaching 86.7%. Overall, both systems demonstrated high accuracy rates; however, GPT-4 provided fewer incorrect answers and more accurate responses compared to GPT-3.5. Furthermore, GPT-4 achieved higher scores than GPT-3.5 in both general knowledge and diagnosis and treatment and follow-up categories. GPT-3.5, on the other hand, predominantly received moderate scores in the general knowledge-diagnosis category and demonstrated a broader distribution of scores in the treatment-follow-up category. In our study, although not statistically significant, ChatGPT-4 demonstrated better performance than ChatGPT-3.5 by providing more comprehensive answers. This suggests that ChatGPT-4 has the potential to be an effective supportive tool in diagnostic, therapeutic, and clinical decision-making processes related to testicular cancer. However, both models exhibited limitations in answering certain questions. This finding underscores the importance of human oversight when employing AI applications, particularly in healthcare-related topics. The study also emphasizes the importance of continuous improvement to ensure the effectiveness and reliability of ChatGPT, a supportive tool used in clinical practice, emphasizing the importance of continuous improvement to ensure its effectiveness and reliability in assisting healthcare professionals with diagnostic and therapeutic decision-making processes. Although ChatGPT-4 demonstrates significant advancements in providing responses to questions related to testicular cancer, the best use cases and ethical considerations have not yet been fully clarified. Further detailed studies are required to determine whether these models can reliably serve as clinical aids in medical practice.

Study Limitations

This study focuses exclusively on testicular cancer, which limits the generalizability of its findings to other oncological or urological conditions. Although the responses were evaluated by experts, variability in assessments may occur across different expert panels. In future studies, we aim to obtain more objective results by including evaluations from independent urologists and employing consensus-based approaches such as the Delphi method. Additionally, the model was tested solely using the 2023 EAU guidelines and clinical experience. Incorporating additional authoritative sources-such as the American Urological Association guidelines, Campbell-Walsh Urology, Smith & Tanagho's General Urology, and other prominent urological guidelines and reference texts-may enhance the model's accuracy and comprehensiveness. The subscription-based structure and limited accessibility of the platform may also pose a barrier for users with constrained resources. Furthermore, it remains unclear whether the EAU guidelines were directly included in ChatGPT's training data, which may limit the alignment of its responses with these guidelines.

Conclusion

Although ChatGPT-4 provides more accurate and satisfactory responses compared to ChatGPT-3.5 in specific urological topics such as testicular cancer, it is not entirely flawless. Its occasional blending of correct and incorrect information may pose risks for healthcare professionals. This highlights the necessity of expert validation and supervised systems in the integration of AI-based models into clinical practice. In this context, it is evident that such technologies should be positioned solely as supportive tools. In the future, the development of customized AI systems trained exclusively on urology-specific data, by leveraging open-source LLMs (e.g., DeepSeek, LLaMA, Mistral), may enable the creation

of more reliable, specialized, and clinically applicable AI solutions. This approach could enhance accuracy and trustworthiness, particularly in niche areas such as testicular cancer. The present study may serve as a foundational step toward the development of urology-specific LLMs. Ultimately, this could contribute to the creation of more tailored solutions that support the safe, ethical, and effective use of AI in healthcare.

Ethics

Ethics Committee Approval: This study did not involve any human subjects or health data; therefore, ethical approval was not required.

Informed Consent: This study did not include any human subjects or health data, patient consent was not required.

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Footnotes

Authorship Contributions

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

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Original Article

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Scrotal Pain in Testicular Cancer: Analysis of Its Association with Clinicopathological Features

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Abstract

Objective: In our study, we aimed to determine the prevalence of scrotal pain at initial presentation in patients with testicular cancer (TC) and to investigate the association of scrotal pain with the clinical, histological, and pathological features of TC.
Materials and Methods: Patients who underwent radical inguinal orchiectomy with a pathology of TC between 2015 and 2024 at two training and research hospitals were retrospectively analyzed. Data on patients' age, initial presenting complaints, side of cancer, preoperative alpha-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase levels, stage, presence of rete testis/lymphovascular/hilar invasion, tumor size, number of tumor foci, and histological subtypes were recorded. Patients were categorized into two groups based on whether they reported scrotal pain at the initial presentation. The relationship between scrotal pain and the aforementioned factors was statistically analyzed.
Results: A total of 129 patients with TC were included, 63 (48.8%) reporting scrotal pain and 66 (51.2%) without pain. The primary complaints at presentation were-62 patients (48.1%) with painless scrotal swelling/irregularity, 48 patients (37.2%) with painful scrotal swelling/irregularity, and 15 patients (11.6%) with scrotal pain only. Additionally, two patients (1.6%) were diagnosed after abdominal masses were detected on computed tomography for abdominal pain, one (0.8%) was diagnosed during imaging for flank pain, and one (0.8%) was diagnosed during an infertility workup with scrotal ultrasonography. The mean age of the patients was 34 years. Pathology showed 61 (47.3%) seminoma and 68 (52.7%) non-seminoma cases. Rete testis invasion was present in 36 (27.9%) of cases and absent in 93 (72.1%) of cases. Lymphovascular invasion was present in 40 patients (31%) and absent in 89 patients (69%). Cancer staging classified 77 (59.7%) as stage 1, 42 (32.6%) as stage 2, and 10 (7.8%) as stage 3. Statistical analysis showed no significant association between scrotal pain and examined factors ($p>0.05$).
Conclusion: The signs and symptoms of TC should be well understood by all male patients and clinicians. It is important to keep in mind that scrotal pain can be observed in nearly half of TC patients. Prospective studies involving larger populations are needed to better understand the relationship between scrotal pain and TC.
Keywords: Orchiectomy, pain, signs and symptoms, testis cancer

Introduction

In recent years, there has been a significant increase in the incidence of testicular cancer (TC), particularly in industrialized societies, although the exact cause remains unclear. The incidence of TC peaks in the 20-40 age range, making it one of the most commonly diagnosed cancers in men within this age group (1,2). If diagnosis and treatment are initiated early in the development of TC, the five-year survival rate for patients can reach up to 99%. Although treatment options have significantly advanced, the survival rate for patients diagnosed at the metastatic stage of TC can decrease to as low as 78%. Furthermore, patients undergoing chemotherapy are at a high risk of experiencing side effects that could impact their quality of life (2-4). To prevent late diagnosis in TC patients, it is crucial that all men, as well as clinicians, are familiar with the signs and symptoms of TC (4,5). As stated in the European Association of Urology (EAU) guidelines, the general consensus in the literature is that TC is typically diagnosed as a "painless testicular mass or an incidental finding on ultrasound (US)" (6). A review of

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previous literature shows that scrotal pain is reported in only 0.01-10% of TC cases (7). Additionally, TC is listed under "painless masses" in the guidelines for primary healthcare services, that patients first approach (8). However, recent studies emphasize that pain can be a common symptom in patients with TC (2,7,9). The cause of scrotal pain in TC is thought to be related to hemorrhage or infarction within the tumor (7). A key topic of debate in the research is whether the presence of scrotal pain in TC can predict or reflect the stage of the cancer.

In our study, we aimed to determine the prevalence of scrotal pain at the time of initial presentation in patients with TC and investigate the relationship between scrotal pain and the clinical, histological, and pathological features of TC.

Materials and Methods

Our research was initiated after obtaining approval from the Scientific Research Evaluation and Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2024-834, date: 11.09.2024). The data of patients who underwent radical inguinal orchiectomy with a preliminary diagnosis of TC between January 2015 and January 2024, at Dışkapı Yıldırım Beyazıt Training and Research Hospital and University of Health Sciences Türkiye, Ankara Etlik City Hospital were retrospectively reviewed from the hospital's information management system. Patients under the age of 18, those with a pathological diagnosis other than TC, sex cord stromal or adnexal tumors, primary extragonadal tumors, those who underwent orchiectomy due to an extratesticular mass, undescended testis, partial orchiectomy, a history of previous TC; and those with incomplete data in the records were excluded from the study. The surgical decisions for all patients were made by specialized urologists based on physical examination, scrotal Doppler US, tumor markers, and, when necessary, magnetic resonance imaging results. Additionally, all patients were provided with information about the inguinal orchiectomy procedure, and written consent was obtained.

We analyzed patients' age, cancer laterality, preoperative levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH), contrast-enhanced thoracoabdominal computed tomography findings, and histopathological reports, including histological subtypes (seminoma vs. non-seminoma), tumor sizes (mm), number of tumor foci (unifocal or multifocal), and the presence of rete testis, lymphovascular, or hilar invasion. The pathological stage and prognostic groups of the patients were determined according to the 2016 tumor, node, metastasis (TNM) classification system of the International Union Against Cancer (10). Additionally, the initial complaints of patients presenting to the emergency department or urology outpatient clinic were reviewed. However, in patients who reported scrotal pain at initial presentation, the severity of the pain could not be quantified due to the retrospective design of our study.

Statistical Analysis

Descriptive statistics were used to report the characteristics of the study groups, which were classified based on the presence or absence of scrotal pain. Continuous variables and their distribution patterns were evaluated for normality using the Shapiro-Wilk test. Variables that did not meet the assumptions for parametric tests were reported as medians and interquartile ranges (Q1-Q3) and compared using the Mann-Whitney U test. Categorical variables were summarized as frequency distributions and percentages, and comparisons were made using chi-square tests. In our study, a type 1 error level of 0.005 was considered, and all analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, New York, United States of America).

Results

Following a review of the information management systems of our hospitals, data from 163 patients were collected. After applying the exclusion criteria, data from 129 patients with TC were included in the analysis. Among these, 63 patients (48.8%) reported scrotal pain at their initial presentation, while 66 patients (51.2%) did not experience pain. The primary complaints at presentation were identified as follows: 62 patients (48.1%) had painless scrotal swelling or irregularity, 48 patients (37.2%) had painful scrotal swelling or irregularity, and 15 patients (11.6%) presented with scrotal pain only. Additionally, 2 patients (1.6%) were diagnosed after abdominal masses were detected on computed tomography performed for abdominal pain, and 1 patient (0.8%) received a diagnosis during imaging performed due to flank pain. Lastly, 1 patient (0.8%) was diagnosed with a TC during an infertility workup involving scrotal Doppler ultrasonography. The initial presenting complaints of the patients are summarized in Table 1.

The mean age of the patients was calculated as 34 years [standard deviation (SD): ±11.84; median: 30 (Q1: 25, Q3: 40)]. TC was located in the right testis in 67 (51.9%) patients; in the left testis in 62 (48.1%) patients; with no cases of bilateral TC. The preoperative mean AFP level was 351.1 ng/mL SD: ±1693.3, median: 3.7 (Q1: 2.21, Q3: 53.65), hCG level was 2224.7 mIU/mL (SD: ±23233.94, median: 1.74 (Q1: 0.2, Q3: 31.79), and LDH level was 392.5 U/L (SD: ±1170.11, median: 221 (Q1: 190.75, Q3: 229.5).

Pathologically, the mean tumor size was 43.4 mm [SD: ±23.7; median: 40 (Q1: 25, Q3: 58.5)]. Among the patients, 61 (47.3%) were diagnosed with seminoma, while 68 (52.7%) had non-seminoma histology. Tumors were unifocal in 105 (81.4%) patients and multifocal in 24 (18.6%). Rete testis invasion was present in 36 (27.9%) patients, while 93 (72.1%) patients had

Table 1. Initial presenting complaints of patients with testicular cancer

Complaints	**(n, %)**
Painless scrotal swelling-irregularity	**62 (48.1%)**
Painful scrotal swelling-irregularity	**48 (37.2%)**
Only scrotal pain	15 (11.6%)
CT for abdominal pain	2 (1.6%)
CT for flank pain	1 (0.8%)
USG for infertility	1 (0.8%)
CT: Computed tomography, USG:Ultrasonography	

no invasion. Lymphovascular invasion was detected in 40 (31%) patients and was absent in 89 (69%). Additionally, hilar invasion was present in 13 (10.1%) patients, and absent in 116 (89.9%).

Based on the TNM staging system, the prognostic classification results were as follows: 77 (59.7%) patients were stage 1, 42 (32.6%) were stage 2, and 10 (7.8%) were stage 3. The clinical and pathological data of the patients are summarized in Table 2.

The relationship between scrotal pain and various clinical and pathological factors was analyzed. Statistical evaluations showed no significant association between scrotal pain and patient age, tumor laterality, tumor size, number of tumor foci, presence of rete testis invasion, lymphovascular invasion, hilar invasion, preoperative AFP, hCG, LDH levels, disease stage, and histological subtype of the tumor (p-values: 0.188, 0.725, 0.532, 0.501, 0.237, 0.848, 0.763, 0.728, 0.948, 0.296, 0.303, and 1, respectively). Detailed statistical results are presented in Table 3.

Table 2. Clinical and pathological information of patients with testicular cancer

Age (years) (median: Q1-Q3)	30 (25-40)
Side (n, %)	
Right	67 (51.9%)
Left	62 (48.1%)
Scrotal pain (n, %)	
Absent	66 (51.2%)
Present	63 (48.8%)
Total tumor size (mm) (median: Q1-Q3)	40 (25-58.5)
Number of tumors (n, %)	
Single	105 (81.4%)
Multiple	24 (18.6%)
Rete testis invasion (n, %)	
Absent	93 (72.1%)
Present	36 (27.9%)
Lymphovascular invasion (n, %)	
Absent	89 (69%)
Present	40 (31%)
Hilus invasion (n, %)	
Absent	116 (89.9%)
Present	13 (10.1%)
AFP (ng/mL) (median: Q1-Q3)	3.7 (2.21-53.65)
hCG (mIU/mL) (median: Q1-Q3)	1.74 (0.2-31.79)
LDH (U/l) (median: Q1-Q3)	221 (190.75-229.5)
Stage (n, %)	
1	77 (59.7%)
2	42 (32.6%)
3	10 (7.8%)
Histology (n, %)	
Seminoma	61 (47.3%)
Non-seminoma	68 (52.7%)

Q1: 1st quartile, Q3: 3rd quartile, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, mIU: Milli-international unit, U/l: Unit per liter

Discussion

With advancements in modern diagnostic and treatment methods, TC exhibits one of the highest survival rates among all cancer types, however, delays in diagnosis often result in the detection of TC at more advanced clinical stages. Consequently, this necessitates intensive chemotherapy, leading to increased morbidity and mortality that is associated with the TC (4). According to the United States National Cancer Institute's Surveillance, Epidemiology, and End Results database, the

Table 3. Statistical analysis of possible factors causing scrotal pain in testicular cancer

Factors	Scrotal pain		p-value
	Absent	**Present**	
Age (years) (median; Q1-Q3)*	29.5 (24-40)	35 (25-41)	0.188
Side (n, %)			0.725
Right	33 (49.3%)	34 (50.7%)	
Left	33 (53.2%)	29 (46.8%)	
Total tumor size (mm) (median; Q1-Q3)*	40 (29.5-60)	40 (22-55)	0.532
Number of tumors (n, %)			0.501
Single	52 (49.5%)	53 (50.5%)	
Multiple	14 (58.3%)	10 (41.7%)	
Rete testis invasion (n, %)			0.237
Absent	**45 (48.4%)**	**48 (51.6%)**	
Present	21 (58.3%)	15 (41.7%)	
Lymphovascular invasion (n, %)			0.848
Absent	**47 (52.8%)**	**42 (47.2%)**	
Present	19 (47.5%)	21 (52.5%)	
Hilus invasion (n, %)			0.763
Absent	**59 (50.9%)**	**57 (49.1%)**	
Present	7 (53.8%)	6 (46.2%)	
AFP (ng/mL) (median; Q1-Q3)*	3.84 (2.22-51.36)	3.64 (2.14-60.4)	0.728
hCG (mIU/mL) (median; Q1-Q3)*	1.9 (0-36.3)	0.98 (0.2-14.7)	0.948
LDH (U/l) (median; Q1-Q3)*	232 (195-308)	219 (184.5-299)	0.296
Stage (n, %)			0.303
1	**36 (46.8%)**	**41 (53.2%)**	
2	25 (59.5%)	17 (40.5%)	
3	5 (50%)	5 (50%)	
Histology (n, %)			1
Seminoma	**34 (55.7%)**	**27 (44.3%)**	
Non-seminoma	32 (47.1%)	36 (52.9%)	

*: Mann-Whitney U test, Q1: 1st quartile, Q3: 3rd quartile, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, mIU: Milli-international unit, U/l: Unit per liter
Chi-square test

prognosis of TC worsens as the stage at diagnosis becomes more advanced (11). When TC manifests with pain, it may be misdiagnosed as more prevalent benign conditions, like epididymo-orchitis or scrotal trauma, leading to potential delays in its diagnosis. A survey conducted among patients diagnosed with TC revealed that 95% initially sought care from family physicians, and 54% were misdiagnosed at the time of their initial presentation. A broader study reported a misdiagnosis rate of 13% in primary care centers. In both studies, TC was most commonly mistaken for epididymitis (4,12). These findings highlight a lack of adequate awareness regarding the symptoms of TC, one of the most common malignancies in young men, among both patients and primary care physicians.

Our study demonstrated that, contrary to common belief, scrotal pain is not a rare symptom in patients with TC. In addition to scrotal pain being the sole complaint in some cases, nearly half of the patients with TC experienced this symptom. Similar to our findings, Rovito et al. (2) in a survey involving 569 TC patients, reported that 44.3% of their patients experienced scrotal pain during the initial clinical examination. Additionally, Wilson and Cooksey (7) emphasized the significance of scrotal pain as a symptom in TC patients. Although some previous studies have reported lower rates of scrotal pain, they also concluded that scrotal pain is not a rare occurrence in patients with TC (12,13). Although the EAU guidelines describe TC as a "painless testicular mass or an incidental finding on US" in our study, only one patient was diagnosed incidentally with TC during scrotal ultrasonography performed for another reason (6).

The number of studies investigating the mechanism by which TC causes scrotal pain is limited. Similar to our findings, Wilson and Cooksey (7) did not find a significant relationship between the presence of scrotal pain at presentation and the histological subtype or stage of TC. On the other hand, Rovito et al. (2) reported that the frequency of scrotal pain increases as the stage of TC advances. Our study is the first to examine the relationship between scrotal pain at initial presentation and TC-specific factors such as tumor size, number of tumor foci, rete testis invasion, lymphovascular invasion, hilar invasion, preoperative AFP, hCG, and LDH levels. In our study, we found that the presence of scrotal pain does not predict the presence of TC-specific factors.

An increasing number of healthcare consumers are turning to the internet as a primary source of information, with many individuals considering online searches as a step that precedes consulting a physician (14). Particularly among younger patients, the internet is highly likely to serve as a key source of health-related knowledge. Therefore, understanding which websites patients access, how they filter the information, and what criteria they use to assess its reliability is crucial, as it ultimately affects the quality of the information obtained. Given these factors, it is reasonable to anticipate that suspicions regarding a potential cancer diagnosis may lead to heightened anxiety.

Pain, including cancer-related pain, is now widely recognized as a complex biopsychosocial phenomenon influenced by multiple factors (15). Cancer pain may stem from a variety of biological factors, including both disease-related and treatment-related mechanisms (16). However, it is not limited to purely physiological or biological causes; psychological elements such as anxiety and fear also play a significant role in shaping the pain experience (17). In our current study, while clinical and pathological factors associated with pain were examined, no psychometric tools were used to assess psychological contributors. The high frequency of reported pain may be a psychosomatic manifestation triggered by anxiety associated with the possibility of a testicular tumor diagnosis.

Study Limitations

Since our study was conducted retrospectively using the hospital information management system, the severity of scrotal pain could not be assessed. Consequently, the relationship between the degree of scrotal pain severity and the stage of TC could not be evaluated. Moreover, the impact of initial scrotal pain on the prognosis of TC patients could not be investigated during follow-up. Another limitation of our study is the lack of evaluation of individual tumor components such as yolk sac and teratoma, as well as pathological findings that may contribute to scrotal pain, such as necrosis and infarction.

Conclusion

In conclusion, the signs and symptoms of TC should be well understood by all male patients and clinicians. It is important to keep in mind that scrotal pain may be present in approximately half of patients with TC. Prospective studies involving larger populations are needed to better understand the relationship between scrotal pain and TC.

Ethics

Ethics Committee Approval: Scientific Research Evaluation and Ethics Committee of University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2024-834, date: 11.09.2024).

Informed Consent: All patients were provided with information about the inguinal orchiectomy procedure, and written consent was obtained.

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Footnotes

Authorship Contributions

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Original Article

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Association of ASA Score with Postoperative Complications in Uro-oncological Surgeries: A Retrospective Comparative Analysis of ASA 1-2 and ASA 3-4 Patients

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Abstract

Objective: This study aims to compare perioperative adverse effects between patients classified as American Society of Anesthesiologists (ASA) 1-2 and ASA 3-4 undergoing major oncological urological surgeries. It also evaluates the impact of ASA classification on surgical outcomes.

Materials and Methods: A retrospective analysis was conducted on patients who underwent open, laparoscopic, or robotic surgery for bladder, kidney, ureter, and prostate cancer between 2022 and 2024. Patients were categorized into two groups: ASA 1-2 (group 1) and ASA 3-4 (group 2). Perioperative complications were classified using the Clavien-Dindo grading system, focusing on grade 4-5 complications. Statistical analyses were performed using chi-square and Mann-Whitney U tests, with $p<0.05$ considered statistically significant.

Results: A total of 367 patients were included in the study: 198 radical prostatectomy cases, 76 nephrectomy cases, 41 partial nephrectomy cases, 30 cystectomy cases, and 22 nephroureterectomy cases. Of these, 198 patients were classified as ASA 1-2, while 169 were ASA 3-4. Grade 4-5 complications included pulmonary embolism, sepsis, myocardial infarction, atrial fibrillation, disseminated intravascular coagulation, and death. However, there was no statistically significant difference in the incidence of major complications between ASA groups across different surgical procedures ($p>0.05$).

Conclusion: Despite the expectation of higher complication rates in ASA 3-4 patients, no significant difference was observed between ASA-groups in perioperative adverse effects. This finding suggests that optimized perioperative management and advanced surgical techniques may mitigate the impact of ASA classification on surgical outcomes in oncological urology.

Keywords: Bladder tumor, oncologic outcomes, prostate cancer

Introduction

Perioperative adverse effects are critical determinants of surgical outcomes, particularly in oncological urology, where patient comorbidities significantly influence both immediate and long-term results (1). The American Society of Anesthesiologists (ASA) classification system provides a standardized method to assess the physical status of patients prior to surgery. ASA scores ranging from 1 to 2 indicate a low risk for surgical complications, while scores of 3 to 4 reflect moderate to severe systemic disease, suggesting a higher likelihood of perioperative challenges (2). Understanding how these classifications correlate with adverse effects is essential for improving patient safety and optimizing surgical protocols.

In oncological urology, where patients often present with complex medical histories and various comorbid conditions, the perioperative period is particularly vulnerable to complications such as infection, bleeding, and prolonged recovery times. Studies have shown that higher ASA scores are associated with increased rates of perioperative complications, which can impact not only the surgical outcome but also the overall survival and quality of life of cancer patients (3). In oncological urology, specifically, several studies have demonstrated that ASA classification is a significant predictor of morbidity and mortality following procedures such as radical cystectomy or nephroureterectomy (4,5). Therefore, it is imperative to investigate the differences in perioperative adverse effects between patients classified as ASA 1-2 and those classified as ASA 3-4.

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This study aims to conduct a comparative analysis of perioperative adverse effects experienced by ASA 1-2 and ASA 3-4 patients undergoing oncological urological surgeries.

Materials and Methods

In this retrospective study, patients who underwent open, laparoscopic, or robotic surgery for urological oncological malignancies between 2022 and 2024 were evaluated. The ethics committee approval number was provided by the University of Health Sciences Türkiye, Etlik City Hospital Ethics Committee (approval no: AEŞH-BADEK-2024-1172, date: 11.12.2024).

All surgeries were performed by an experienced surgical team at our center, which has completed the learning curve, as evidenced by achieving the case volumes recommended in the literature to ensure procedural proficiency across various urological oncologic operations. Patients' decisions regarding open, laparoscopic, and robotic surgery were made based on the advantages and disadvantages of each approach, following a mutual exchange of information and a decision-making process, between the patients and the surgical team.

Patients with bladder, kidney, ureter, and prostate cancer in ASA 1-2-3, and 4 groups were included in the study. All collected data were analyzed to obtain demographic details, baseline tumor characteristics, perioperative surgical outcomes, perioperative and postoperative complications, and follow-up information. Patients with missing data and those whose follow-up was not conducted at our center were not included in the study. Each patient who underwent oncological surgery was categorized according to the ASA classification system, using the preoperative anesthesiologist evaluation form for this purpose (2).

Preoperative Optimization and Perioperative Care Protocols

Additionally, preoperative optimization strategies were implemented for patients in higher ASA categories, including nutritional support, management of comorbidities, optimization of cardiovascular and respiratory function, and the use of thromboprophylaxis. We administered Clexane for one month, and determined its use based on the patient's comorbidities and specific condition through consultations with relevant specialists. These measures aimed to reduce perioperative complications and improve postoperative recovery. Postoperative care protocols focus on early mobilization, pain management, thrombosis prevention, and monitoring for potential complications to ensure optimal recovery and long-term outcomes.

Evaluation of Adverse Events

To evaluate the safety of surgical procedures, perioperative complications were classified using the Clavien-Dindo grading system (6). The assessment of surgical safety focused primarily on complications graded as 3 or higher, which are considered major adverse events. In this classification, grade 1 complications include any deviation from the typical postoperative course that does not require therapeutic intervention, with the exception of certain medications (e.g., antiemetics, analgesics, and antipyretics). Grade 2 complications involve adverse events that necessitate pharmacological treatment or blood transfusion. Complications managed with interventions performed under anesthesia also fall under grade 3. More severe complications, such as those arising from pneumoperitoneum or the Trendelenburg position, are categorized as grade 4 or grade 5.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 for Windows. Categorical variables were evaluated using the chi-square (χ^2) test, and Fisher's exact test was applied when small sample sizes were encountered. Statistical significance was defined as a p-value of less than 0.05.

Results

A total of 30 cystectomy patients have been included in the study. Among these patients, 14 belong to ASA 1-2 (group 1), while the remaining 16 belong to ASA 3-4 (group 2). It consists entirely of patients who underwent open radical cystectomy.

A total of 76 patients who underwent nephrectomy were included in the study. Among these patients, 54 were classified as ASA 1-2 (group 1), while the remaining 22 were classified as ASA 3-4 (group 2). Out of the 76 patients, 52 underwent laparoscopic nephrectomy, and 24 underwent open nephrectomy.

A total of 41 patients who underwent partial nephrectomy were included in the study. Among these patients, 17 were classified as ASA 1-2 (group 1), while the remaining 24 were classified as ASA 3-4 (group 2). Among these 41 patients, 26 underwent open partial nephrectomy, and 15 underwent laparoscopic partial nephrectomy.

A total of 22 patients who underwent nephroureterectomy were included in the study. Among these patients, 9 were classified as ASA 1-2 (group 1), while the remaining 13 were classified as ASA 3-4 (group 2). Among these 22 patients, 16 underwent laparoscopic nephroureterectomy, and 6 underwent open nephroureterectomy.

A total of 198 patients who underwent radical prostatectomy were included in the study. Among these patients, 104 were classified as ASA 1-2 (group 1), while the remaining 94 were classified as ASA 3-4 (group 2). Among these 198 patients, 34 underwent open prostatectomy, and 164 underwent robotic prostatectomy.

Grade 4-5 Complications

Grade 4 to 5 complications occurred among the patients who underwent cystectomy. One patient had a pulmonary embolism (PE), one developed sepsis, one had a myocardial infarction, and one experienced disseminated intravascular coagulation (DIC). The patient with DIC died due to the condition. The patient with DIC was in ASA 3-4 (group 2), while the remaining complications occurred in patients from group 1. There was no statistically significant difference between the two groups (p=0.74). The patient data are summarized in Table 1.

In the nephrectomy group, atrial fibrillation (AF) developed in one patient from ASA 1-2 and one patient from ASA 3-4. PE occurred in one patient from each group. Additionally,

one patient from the ASA 1-2 group developed sepsis due to pneumonia. There was no statistically significant difference between the two groups (p=0.81).

In the partial nephrectomy group, one patient in group 1 developed AF, another had a PE, and another experienced DIC. The patient with DIC, who belonged to the ASA 3-4 group, died due to the condition. There was no statistically significant difference between the two groups (p=0.67).

In the nephroureterectomy group, only one patient required three days of intensive care support due to desaturation. This patient belonged to the ASA 3-4 (group 2) category.

Among the patients who underwent radical prostatectomy, 2 developed PE, 1 had arterial thrombosis-related cerebrovascular occlusion, 1 developed sepsis, 1 had myocardial infarction, and 2 experienced new-onset AF. One patient with PE was from group 1, and the other was from group 2. Sepsis and myocardial infarction occurred in group 1, while both cases of AF were in group 2. There was no statistically significant difference between the two groups (p=0.68). Complications are summarized in Table 2.

Discussion

Perioperative adverse effects are critical considerations in oncological urology, where surgical complexity and patient comorbidities significantly impact outcomes. Our study aimed to compare perioperative complications among patients with ASA 1-2 and ASA 3-4 classifications undergoing major urological cancer surgeries. Our findings indicate that higher ASA scores are not associated with a statistically significant increase in perioperative complications.

The ASA classification system is widely used to predict perioperative risk, with studies consistently demonstrating that patients with ASA 3-4 scores experience greater postoperative morbidity and mortality (2). However, in our study, while complications such as PE, sepsis, myocardial infarction, AF and DIC were observed, there was no significant difference between the two ASA groups in most surgical categories. This finding aligns with recent literature suggesting that surgical outcomes are influenced by a combination of factors beyond ASA classification alone, including surgical technique, intraoperative management, and perioperative care protocols.

Several studies have analyzed the impact of ASA scores on perioperative complications in various surgical disciplines.

Table 1. Summary of patients undergoing urological oncological surgeries

Surgery	Total patients	ASA 1-2 (group 1)	ASA 3-4 (group 2)	Open surgery	Laparoscopic surgery	Robotic surgery
Radical cystectomy	30	14	16	30	0	0
Nephrectomy	76	54	22	24	52	0
Partial nephrectomy	41	17	24	26	15	0
Nephroureterectomy	22	9	13	6	16	0
Radical prostatectomy	198	104	94	34	0	164

ASA: American Society of Anesthesiologists

Table 2: Summary of grade 4-5 complications

Surgical procedure	Complication	ASA 1-2 (group 1)	ASA 3-4 (group 2)	p-value
Cystectomy	Pulmonary embolism	1	0	0.74*
	Sepsis	1	0	
	Myocardial infarction	1	0	
	Disseminated intravascular coagulation (DIC)	0	1 (exitus)	
Nephrectomy	Atrial fibrillation (AF)	1	1	0.81*
	Pulmonary embolism	1	1	
	Sepsis (due to pneumonia)	1	0	
Partial nephrectomy	Atrial fibrillation (AF)	1	0	0.67*
	Pulmonary embolism	1	0	
	Disseminated ıntravascular coagulation (DIC)	0	1 (exitus)	
Nephroureterectomy	Intensive care support (desaturation)	0	1	-
Radical prostatectomy	Pulmonary embolism	1	1	0.68*
	Arterial thrombosis-related CVO	1	0	
	Sepsis	1	0	
	Myocardial infarction	1	0	
	Newly onset atrial fibrillation (AF)	0	2	

*chi-square (χ^2) test, and Fisher's exact test, ASA: American Society of Anesthesiologists, CVO: Cerebrovascular occlusion

A meta-analysis found that ASA scores strongly correlated with postoperative morbidity and mortality across multiple surgical specialties (7). Specifically, in oncological urology, higher ASA scores have been linked to increased postoperative complications, prolonged hospital stays, and higher rates of intensive care unit admission. However, some studies suggest that with optimized perioperative management, even ASA 3-4 patients can achieve favorable surgical outcomes, which is in line with our findings (8).

In a study, the authors found that ASA classification alone was a moderate predictor of complications, with other factors such as intraoperative hemodynamic stability, blood loss, and anesthesia type playing equally important roles. In our study, despite the expectation of higher complication rates in the ASA 3-4 patients, the observed complication rates were not significantly different between groups (9). This may be due to the rigorous perioperative care protocols implemented at our center, which include preoperative optimization, intraoperative monitoring, and aggressive postoperative management.

One potential explanation for the lack of statistical significance in complication rates is the evolving nature of surgical techniques. With advancements in laparoscopic and robotic surgery, perioperative morbidity has been substantially reduced. In our study, the majority of radical prostatectomies were performed using a robotic approach, which is associated with lower blood loss, reduced complications, and shorter hospital stays compared to open surgery (10). Similarly, laparoscopic nephrectomy and nephroureterectomy have demonstrated superior perioperative outcomes in various studies, which may contribute to the relatively low complication rates in our cohort.

Several studies have highlighted the benefits of minimally invasive surgery in high-risk patients. A paper compared laparoscopic and open nephrectomy outcomes in patients with high ASA scores and found that laparoscopic surgery was associated with significantly lower rates of complications and faster recovery (11). The predominance of minimally invasive techniques in our study could explain the relatively comparable complication rates between ASA groups.

Despite the absence of statistically significant differences between groups, it is important to consider the impact of individual complications. PE was observed in multiple patients, with at least one case in each ASA group across different surgical procedures. Studies indicate that thromboembolic events are among the leading causes of postoperative morbidity in urological oncology (12). The use of perioperative thromboprophylaxis, early mobilization, and intraoperative monitoring is a crucial strategy to mitigate this risk. The relatively even distribution of PE across ASA groups in our study suggests that while baseline health status plays a role, intraoperative and postoperative factors such as anticoagulation protocols and patient mobilization are equally important.

Sepsis was observed in multiple cases, particularly in patients undergoing cystectomy and nephrectomy. The presence of pre-existing infections, prolonged surgical duration, and urinary tract instrumentation is a key risk factor. Our study supports previous findings that patients with ASA 3-4 scores are at an increased risk of severe infections due to immunosuppression and comorbidities, even though the overall incidence did not significantly differ between groups.

AF was recorded in both nephrectomy and radical prostatectomy patients, with a higher incidence in ASA 3-4 patients. New-onset AF is a well-recognized postoperative complication, particularly in elderly patients and those with pre-existing cardiovascular disease. While our findings suggest that ASA 3-4 patients may be more prone to AF, the lack of statistical significance may indicate that other perioperative factors, such as fluid management, electrolyte balance, and intraoperative anesthesia protocols, play a more significant role.

DIC was observed in the partial nephrectomy and cystectomy groups among patients classified as ASA 3-4, resulting in mortality. DIC is a severe and often fatal condition characterized by widespread activation of the coagulation cascade. Although rare, its occurrence underscores the importance of vigilant perioperative monitoring and early intervention in high-risk patients.

Study Limitations

Despite its strengths, our study has some limitations. The retrospective nature of the analysis introduces potential biases, including selection bias and incomplete data collection. Additionally, the sample size in certain surgical subgroups is relatively small, which may limit the statistical power to detect differences between ASA groups. Future prospective studies with larger sample sizes are needed to further validate our findings. Another limitation is the lack of detailed intraoperative variables such as estimated blood loss, duration of surgery, and fluid balance, which could provide a more comprehensive understanding of perioperative risk factors. Additionally, long-term outcomes, including cancer-specific survival and overall survival, were not assessed in this study and should be considered in future research.

Our findings have important implications for perioperative management in urological oncology. While ASA classification remains a useful tool for preoperative risk stratification, it should not be the sole determinant of perioperative risk assessment. A comprehensive approach incorporating multimodal risk assessment tools, enhanced recovery after surgery protocols, and individualized perioperative care plans is essential to optimize outcomes.

Further studies are needed to explore additional factors influencing perioperative outcomes, including frailty indices, nutritional status, and prehabilitation strategies. The role of preoperative optimization programs, such as intensive cardiovascular and pulmonary assessments, in high-risk patients should also be investigated.

Conclusion

While higher ASA scores are generally associated with increased perioperative risk, our study found no statistically significant difference in major complications between ASA 1-2 and ASA 3-4 patients undergoing oncological urological surgeries. This may be attributed to the advancements in surgical techniques, perioperative management strategies, and comprehensive patient care protocols. These findings suggest that with

proper preoperative optimization and careful perioperative management, even patients with higher ASA scores can undergo oncological urological surgeries with comparable outcomes. This may influence clinical decision-making by emphasizing the importance of individualized care rather than relying on ASA score alone. Future prospective studies with larger sample sizes and detailed intraoperative data are necessary to further elucidate the relationship between ASA classification and perioperative outcomes in urological oncology.

Ethics

Ethics Committee Approval: The ethics committee approval number was provided by the, University of health Sciences Türkiye, Etlik City Hospital Ethics Committee (approval no: AEŞH-BADEK-2024-1172, date: 11.12.2024).

Informed Consent: A retrospective analysis was conducted on patients who underwent open, laparoscopic, or robotic surgery for bladder, kidney, ureter, and prostate cancer between 2022 and 2024.

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Footnotes

Authorship Contributions

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