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Research Article

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Trimodal bladder-preserving treatment including high-tech radiotherapy in invasive bladder carcinoma-dissertation project with literature review

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Abstract

Over the last two decades, there has been a significant evolution of the complex treatment of the invasive bladder carcinoma (BC), including both surgery methods and high-tech radiotherapy (RT), often combined with chemotherapy (Ch). Different protocols supporting multimodal treatment and the concept of the bladder preservation are currently developed. New high-tech radiation methods were presented combined with Ch to preserve the bladder as a healing alternative to radical cystectomy. The purpose of this overview is to present the place and healing effect of high-tech RT in the contemporary treatment approach to invasive BC.

The expected contributions from this research project are: 1) For the first time in Bulgaria, modern bladder-sparing strategies combine maximal transurethral resection of bladder tumor (TURBT) followed by an induction course of concurrent radiation therapy (RT) and sensitizing chemotherapy will be held. 2) Disease-free survival, overall survival, local control and early radical toxicity in two patient groups after self intensity modulated radiation therapy (IMRT) and after concurrent chemoradiotherapy (CChRT) with VMAT will be analyzed.

It is important to improve the quality of life by preserving the bladder in the invasive bladder carcinoma.

Keywords: Invasive Bladder Carcinoma, Radiotherapy (RT), Bladder Sparing, Three-Dimensional Conformal Radiation Therapy (3D-CRT), Intensity Modulated Radiation Therapy (IMRT), Volumetric-Modulated arc Therapy (VMAT), Concomitant Chemoradiotherapy.

Introduction

The bladder cancer (BC) ranks the tenth place among diagnosed neoplasms thus being a serious health problem. Cancer incidence and mortality are rapidly growing worldwide. The world incidence of BC in 2018 is 550 000. Lebanon is the country with the highest yearly BC incidence rate 25 per 100 000 in the population, followed by Greece/21,2, while Bulgaria ranks at the nineteenth place with yearly incidence rate 12,1 [1]. Despite the significantly lower Bulgarian incidence rate the mortality rate is high reaching one third of the diagnosed men and women [2]. Despite ongoing debates about the optimal primary intervention, radical cystectomy remains the cornerstone of first-line therapy in many institutions. Over the past decade, bladder-preserving strategies involving transurethral resection (TUR), chemotherapy (Ch) and radiotherapy (RT) have evolved [3]. Recent advances in the techniques of radiotherapy planning, verification and delivery offer the possible to overcome obstacles that have previously restricted the achievement of bladder RT [4].

Treatment

The treatment of NMIBC consists of TUR which is a therapeutic method of choice at every initial bladder cancer. Before or after the intravesical therapy a second TUR takes place in highly-risky NMIBC. Due to a high risk of relapse, for multiple T1 (G3) NMIBC with CIS, a radical cystectomy with urine derivation was discussed [9]. For a long time, radical cystectomy was considered as standard MIBC treatment [10]. Due to the rapid worsening of the quality of life among patients [11,12], this operative approach was regarded as a remarkable mutilation, despite the advance of the surgical techniques and the significant reduction of the complications and mortality after radical cystectomy [13,14]. After radical cystectomy, despite the early applied aggressive surgery, among a significant part of the patients with MIBC, a high risk of relapse, often leading to lethal outcome was observed. The

major part of the relapses manifested during the third year after the radical cystectomy, while 75% of the patients die of distant metastases [15].

Radiotherapy (RT)

The RT is an alternative treatment strategy among patients with contraindications for radical cystectomy or in case of unwillingness to undergo such [16,17]. Hayter et al./1999 made an announcement of 20 906 patients with MIBC who were diagnosed and treated with radical RT alone or with radical cystectomy [18]. The five-year specific survival rate after radiotherapy with bladder sparing reached 41% while the 5-year overall survival rate was hardly 25%. An important conclusion of the study is that when analyzing the overall survival after radiotherapy alone and after radical cystectomy, there was no significant difference [18]. The radical RT followed by salvage cystectomy was comparable to the initial cystectomy, but with the important advantage that the bladder function was sustained for a long period of time [19,20].

Neoadjuvant Cisplatin-based combined chemotherapy (NCBCCh)
The standard treatment of MIBC (cT2-T4a N0M0) is NCBCCh followed by radical cystectomy. In Cisplatin-ineligible patients radical cystectomy alone was recommended [21]. NCBCCh improves overall survival and should be offered to eligible ≥ cT2N0 patients [22].

Concurrent Chemoradiotherapy (CChRT)

For muscle-invasive bladder cancer multimodal treatment involving radical cystectomy with neoadjuvant Ch offers the best chance for cure. Selected patients with muscle-invasive tumours can be offered bladder-sparing trimodality treatment consisting of transurethral resection with chemoradiotherapy (ChRT) [23]. ChRT was associated with superior survival compared to RT alone and its uptake corresponded to improved survival among all RT-treated cases in the general population [24]. ASCO endorses the guideline on MIBC and metastatic BC and has added qualifying statements, including highlighting the use of ChRT for select patients with MIBC [21]. Modern bladder-sparing strategies combine maximal transurethral resection of bladder tumor (TURBT) followed by an induction course of concurrent RT and sensitizing Ch [25]. Substantial improvements in local control have more recently been seen with combined modality therapy: transurethral resection of the bladder tumor (TURBT) for debulking followed by RT with concurrent tumor-sensitizing Cisplatin-based Ch [26-30]. A trimodality approach with bladder preservation on the basis of the initial tumor response was, therefore, safe, with most long-term survivors retaining functional bladders [31]. Adjuvant cisplatin-based combination chemotherapy may be considered, particularly for pT3-4 and/or pN+ disease without prior NA chemotherapy. Trimodal bladder-preserving treatment via maximal transurethral resection of bladder tumor followed by concurrent chemoradiation was safe [22]. Combined modality treatment with TURBT, Ch, RT, and selection for organ-conservation by response had a 52% overall survival rate. This result was similar to cystectomy-based studies for patients of similar age and clinical stages [32]. Comparing approaches by TUR plus Ch alone with TURBT plus CChRT, the 5-year survival rates with a preserved bladder for all patients entered ranges from 20-33% when RT was not used and from 41-45% when RT was used. The conclusion was that the combined chemoradiotherapy after TUR increased significantly the relapse-free survival [33]. CCHRT achieves the bladder saving with 67% local tumor control of the eighth year after treatment. Quality of life and quality of bladder function were satisfactory in 67% of patients [34]. The use of CChRT after TURBT (trimodality therapy) increased the probability of surviving and having an intact bladder by 30% to 50% compared with TURBT and Ch alone [31]. The optimal regimen and delivery of CChRT as well as the addition of rational molecular targeted therapy and use of predictive biomarkers continues to be actively investigated within the RTOG and other groups [35,36].

High-tech Radiotherapy

Many working groups develop and sophisticate modern high-tech RT approaches for bladder sparing in BC [8,33]. The bladder sparing with TUR, systemic Ch and RT reaches 60% 5-year survival rate which is approximately equivalent to that after cystectomy and 40% of the patients survive with intact bladder [19].
The 3D-Conformal Radiotherapy (3D-CRT)

Concentrates and directs ionizing radiation towards the tumor target volume so that high enough cancericidal doses with minimal early and late toxicity of normal tissues and organs are produced [4]. The tumor is defined and contoured over each axial CT planning slide, so that a reconstructed three dimensional target volume is produced. The dosimetry planning has the purpose of focusing the ionizing radiation as precise as possible so that the radiation field corresponds to that volume while the nearby normal tissues are screened and protected (Figure 1:A, B). This technique allows an improved dimensional dose distribution but it still cannot completely exclude the normal tissues which are surrounded by the tumor [37].

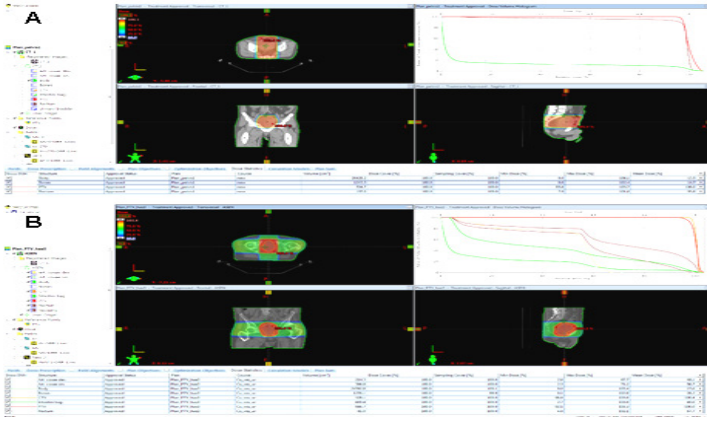

Figure 1: A)B) 3D-conformal radiotherapy in case of invasive bladder carcinoma to total dose (TD) 60 Gy with daily dose (DD) 2 Gy.

The Intensive-Modulated Radiotherapy (IMRT):

It is one of the most important achievements of oncology during the last decade. The benefits of IMRT are correlated to dose escalation, potential for improved locoregional control and anticipated superior treatment results [38]. The improvements of computer technology as well as the visualization techniques allowed the rapid development of this high-tech method [4,37]. IMRT is an advanced technique of high-precision RT that uses computer-controlled linear accelerator to deliver precise radiation doses to a malignant tumor or specific areas within the tumor

[39]. IMRT allows higher radiation doses to be focused to regions within the tumor while minimizing the dose to surrounding normal critical structures [40]. It is an extension of 3D-CRT that allows the delivery of highly complex isodose profiles to the target while minimizing radiation exposure to surrounding normal tissues [41]. Compared to 3D-CRT, where the RT planning is optimized manually, in IMRT dose distribution is inversely determined, meaning that first the treatment planner has to decide on the dose distribution he wants and the computer then calculates a group of beam intensities that will be produced, representing as nearly as possible, the desired dose distribution [42,43]. This technique uses multiple radiation beams of non-uniform intensities. The beams are modulated to the required intensity maps for delivering highly conformal doses of radiation to the treatment targets, while sparing the adjacent normal tissue structures [44]. Since then linear accelerator based IMRT treatment delivery systems that include the binary multi-leaf intensity-modulating collimator (MIMiC) [45], step-and-shoot MLC [46], dynamic MLC (sliding window) [47] and intensity modulated arc therapy (IMAT) [48] have been developed. IMRT allows rapid dose fall-off producing rapid dose gradient along PTV, this characteristic enables delivery of lower dose to critical organs that are in close proximity to the target volume [49]. Figure 2 illustrates IMRT in invasive BC.

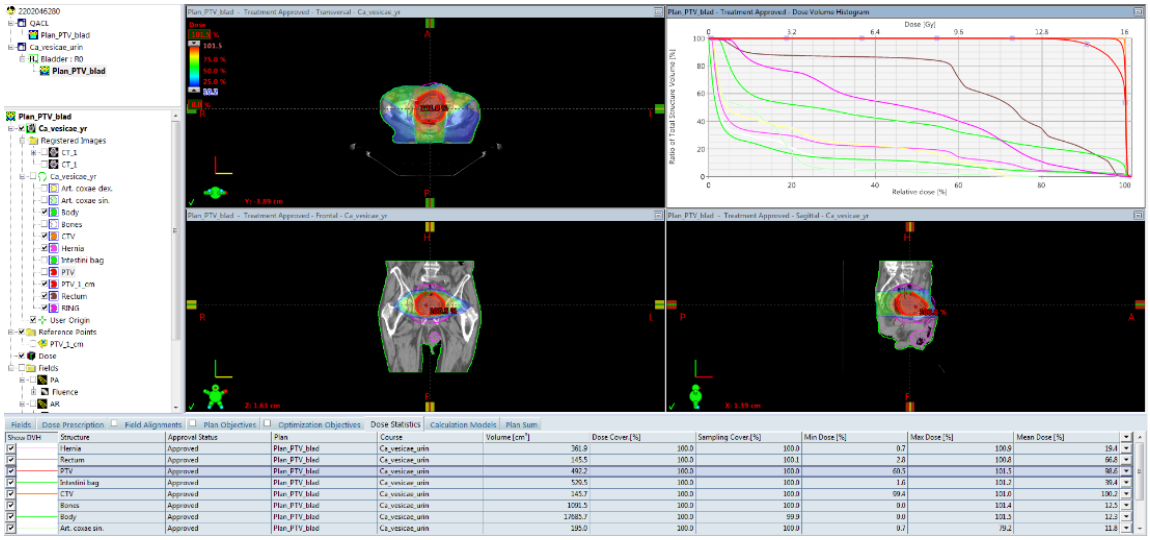

Figure 2: Intensity modulated radiation therapy (IMRT) in case of invasive bladder carcinoma to TD 60 Gy with DD 2 Gy.

The potential disadvantages of the IMRT technique include the increased time which is required for the radiation delivery and thus the risk of filling the bladder which leads to changes in the bladder shape and size. It is proved that the filling degree of the bladder during the radiation is approximately 1 cm3 per minute but with broad variations among patients [50]. Another disadvantage of IMRT is the increased number of monitor units (MU) which is required for the realization of the total dose (TD) which leads to a higher integral tissue dose with potentially higher risk of a secondary malignancy [51]. According to Ruben et al./2008 the effect over the carcinogenesis through the application of lower to medium doses with IMRT technique is minimal [52].

Compared to standard CRT, IMRT techniques give even better shaping of the dose distribution around the tumor with potentially larger reductions in normal tissue late effects and/or larger increases in tumor control [53]. Turgeon et al./2014 present their therapeutic analysis after IMRT with bladder sparing among 24 advanced age MIBC patients [54]. 83% of them achieved local tumor control (LTC), 61% 3-year overall and 71% 3-year specific and 71% 3-year specific survival. On the third year 75% achieved LTC at preserved bladder function. Only 4% of them showed early III stage gastrointestinal and genitourinary toxicity as well as early III and IV stage hematological or liver toxicity. After IMRT, Hsieh et al./2011 achieved median progression-free disease survival for a period of 21 months among 19 patients at median 80-year-old [55].

Volumetric modulated Arc Therapy (VMAT)

Otto in 2007 introduced VMAT as a modified form of IMAT which is able to make variation in dose rate, gantry rotation speed and treatment aperture shapes [38,56]. The biggest advantage of VMAT is its least delivery time and minimum of monitor units (MUs) involved [57]. Figure 3 illustrates VMAT in invasive BC. At VMAT the gentry speed, the position of the multi-leaf collimators (MLC) and the dose power dynamically change during the gantry rotation up to 360 degrees which leads to rapid and highly conformed realization of the RT [58]. As compared to IMRT, treatment time in all cases at 35% to 43% was reduced [59]. VMAT was introduced in clinical practice during the last decade in different malignant neoplasms affecting the brain and the myelon, the head and neck, the carcinomas of the prostate gland, the anal canal, the uterine cervix, etc. [60-62]. The preservation of the normal organs through the usage of VMAT compared with IMRT decreased the early and late radiation toxicity, mostly among patients, demanding local dose addition as well as among those who need combined ChRT and/or Ch afterwards [62].

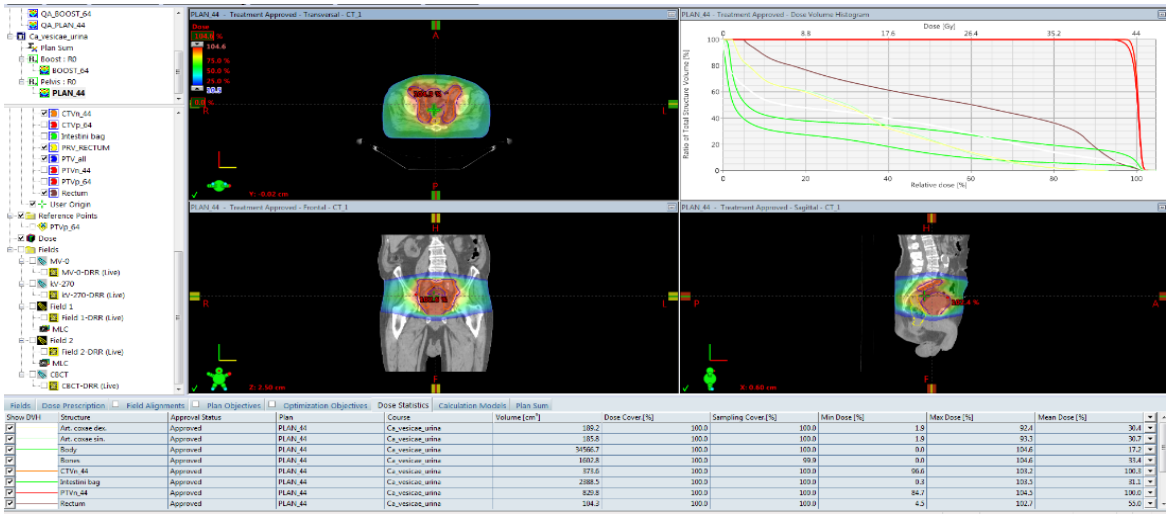

Figure 3: Volumetric-modulated arc therapy (VMAT) in case of invasive bladder carcinoma to TD 60 Gy with DD 2 Gy.

Discussion

Transitional cell carcinoma is the most frequently diagnosed bladder neoplasm, while histological findings such as squamous cell carcinoma, small cell carcinoma and adenocarcinoma are significantly rare [5]. Depending on the involvement of the detrusor muscle the bladder cancer (BC) is classified as muscle invasive (MIBC) or non-muscle invasive (NMIBC) [6]. The muscle invasive bladder cancer (MIBC) (T2-T4) is a potentially serious disease with around 50% long-term survival rate [7,8]. The ideal treatment would be a bladder preserving therapy with total eradication of the tumour without compromising survival [7].

Conclusion

The contemporary radiotherapy techniques 3D-CRT, IMRT and VMAT allow realization of high cancericidal doses as well as a simultaneous preservation of the surrounding normal tissues and organs. The therapeutic efficacy increases at a significant reduced early and late toxicity. Those advantages of the high-tech RT can be combined with the simultaneous application of chemotherapy which sensibilizes the radiation effect. The expected contributions from this research project are: 1) For the first time in Bulgaria, modern bladder-sparing strategies combine maximal transurethral resection of bladder tumor followed by an induction course of concurrent radiation therapy and sensitizing chemotherapy will be held. 2) Disease-free survival, overall survival, local control and early radiation toxicity in two groups, each of which with 40 MIBC after self intensity modulated radiation therapy and after concurrent chemoradiotherapy with VMAT will be analyzed. It is important to improve the quality of life by preserving the bladder in the invasive bladder carcinoma.

The optimization of the radiotherapy combined with the latest systemic therapeutic approaches can allow prospective improvements and the adoption of a strategy for organ preservation for more patients with bladder cancer. Those strategies require full cooperation of urologists, radiation oncologists, medical physicists and medical oncologists.

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