SUMMARY AND GENERAL DISCUSSION

Introduction

This thesis underlines the aggressive nature of bladder cancer. In the Dutch Cancer Registry bladder cancer is reported in the top five of most common tumour localizations in men and in the top ten in women. Nevertheless, the public awareness of this disease is low. Hopefully this thesis may contribute to the awareness among both clinicians and the general population. Furthermore I hope this thesis will improve the multidisciplinary approach to this life-threatening disease.

High-grade non-muscle invasive bladder cancer

High-grade non-muscle invasive bladder cancer (HG-NMIBC) represents a group of urothelial carcinomas with a high risk for recurrence and significant risk of progression to muscle invasive bladder cancer (MIBC). Despite well-defined histo-pathological criteria, there is significant inter-observer variability among pathologists when classifying Ta versus T1 tumours and grading urothelial tumours. Concordance between pathologists ranges from 40-60% for staging (Ta versus T1) and from 70-78% for classifying carcinoma in situ (CIS)[1-3]. Therefore, revision of histo-pathology by a dedicated uro-pathologist has been advised for T1 high-grade tumours (Ta versus T1) and carcinoma in situ (CIS)[4,5].

The study described in **chapter 2** showed that CIS indeed is a disease with a high risk for recurrence (68.9%) and a high rate of progression to muscle invasive bladder cancer (18.9%). In this study the concomitant CIS group appeared to have a poorer prognosis with a shorter duration of bladder preservation and a worse overall survival compared to primary and secondary CIS, although not statistically significant[6]. To

provide another risk profile for CIS of the bladder a different subdivision has been proposed, identifying patients with high-risk CIS (i.e. diffuse CIS, prostatic urethra involvement, over-expression of p53). These patients are to undergo radical cystectomy (RC) without delay in case of BCG failure, whereas those with low-risk CIS (i.e. focal CIS, lack of over-expression of p53) may still be offered bladder-preserving therapy[7]. These results also suggest that early definitive therapy could be advisable in this poor-risk group. CIS of the bladder is also recognized as a risk factor for the development of upper urinary tract tumours after radical cystectomy[8].

The dilemma of bladder-sparing treatment for patients with HG-NMIBC versus early cystectomy has been mentioned earlier. Some reports have been published on the results of early cystectomy for patients with primary CIS. Although the disease-specific survival (DSS) rates in these series are generally excellent (ranging from 85-91%), the rate of overtreatment with early cystectomy is substantial (up to 50% of patients) [9,10]. On the other hand, the window of opportunity to optimally treat these patients with high-risk NMIBC must be taken into account. In a retrospective analysis, the DSS proved to be significantly poorer for patients with progressive MIBC (5-years DSS 28%) versus patients with primary MIBC (5-years DSS 55%)[11,12]. A possible explanation for this worse outcome of patients with progressive MIBC may be found in the fact that high-risk NMIBC tumour biology consists of therapy-sensitive cells and therapy-insensitive cells. Intravesical instillations may lead to selection of resistant cell-lines and a more aggressive tumour biology that subsequently progresses to invasive disease[11]. For high grade T1 disease, early radical cystectomy may be considered for selected high-risk patients (e.g. young patients with multifocal disease, concomitant CIS and tumour in the prostatic urethra, micropapillary UC)[13].

Lymph node staging

In case of progression of NMIBC after conservative treatment or in case of primary MIBC, radical surgery remains the gold standard. As was stated earlier, in case of radical surgery the quality of bilateral pelvic lymph node dissection (PLND) is of the utmost importance[14-16]. The quality of surgical resection is generally measured by the histopathological lymph node count[17,18]. Furthermore lymph node parameters such as lymph node density are used as predictive factors for DSS[19-21]. In **chapter 3** two studies were described concerning this matter. The histopathological outcomes of PLNDs in two different hospitals were compared. These studies show a statistically significant difference between the two pathology departments evaluating the number of lymph nodes after PLND for bladder cancer, despite equal anatomical clearance by the same experienced surgeons. Nevertheless, no statistically significant difference was found in the number of tumour positive lymph nodes. Furthermore there were no differences in overall survival (OS) and recurrence free survival (RFS) between the two hospitals[22,23]. Clearly, next to a thorough anatomic surgical procedure, a standardized histopathological evaluation is of the utmost importance. Unless standardized methods have been agreed upon by pathologists, one should be cautious to use the number of reported lymph nodes as an indicator of the quality of surgery and to use the lymph node density as prognostic factor.

Multimodality treatment in bladder cancer

Nowadays the multidisciplinary approach has generally been adopted as ‘standard of care’ in the field of oncology. Over the years bridges have been built between surgical specialties and the departments of radiotherapy, medical oncology and

pathology to increase the quality of oncological care. Some clinicians may fear these developments, whereas others embrace them in order to go forward. Such a multimodality treatment approach is based on the concept of synergy: “the interaction of elements that when combined produce a total effect that is greater than the sum of the individual elements” (figure 1). This concept of synergy will inevitably be a key facet in improving the outcome of patients with muscle invasive and non-organ confined bladder cancer.

Induction chemotherapy

Multimodality treatment in MIBC consists primarily of neoadjuvant/induction chemotherapy (NIC) followed by surgery or radiation therapy. The study that was reported in **chapter 4** gives an overview of the outcome of patients with non-organ confined bladder cancer who were eligible for surgery and treated with NIC at the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital. Response to chemotherapy was assessed after two cycles based on earlier publications, showing that, in case of no response, further chemotherapy is futile[24]. This study affirms that the prognosis of patients with locally advanced and node positive bladder cancer is generally poor: despite induction chemotherapy and consolidating local therapy median OS was 18 months and the 5-years OS 27.2%. Patients with a complete pathological response to induction chemotherapy after surgery fare significantly better (median OS 74 months and 5-years OS 53.8%). Clinical and pathological response to chemotherapy and the clinical node status after chemotherapy (ycN-status) were significant predictive factors for OS[25].

Most trials investigating the potential benefit of NIC excluded node positive patients, nevertheless hypothetically this group of poor prognosis patients may benefit the most[26]. In the study that was outlined in **chapter 7**, including only node positive patients, one out of four patients showed complete pathological response to NIC with subsequently a significant DSS benefit (median DSS 127 months and 5-years DSS 63.5%). In this series clinical and pathological response to chemotherapy were predictive parameters for outcome. Furthermore, clinically isolated nodal response is associated with a better outcome when compared to isolated local response in the bladder[27]. As was discussed in **chapter 4,** patients with pathologically progressive disease after chemotherapy, who were subjected to total cystectomy performed no better than the patients who did not undergo surgery. Therefore based on these results we do not advise consolidating surgery to patients in our institution with progressive disease during induction chemotherapy. Radiation therapy could be considered as a non-surgical alternative in these patients.

Another issue that is addressed in **chapter 4** concerns the limited reliability of the current imaging techniques with respect to clinical staging. The negative predictive value for clinical staging by current imaging techniques was 62.5%. Meaning that in 37.5% of patients with a complete clinical response after chemotherapy, residual tumour was found at surgery[25]. The introduction of novel imaging modalities such as FDG-PET/CT-scan and diffusion-weighted magnetic resonance imaging (MRI) in the standard workup before and after induction chemotherapy may improve clinical staging[28-30]. The limitations of current imaging techniques are also reflected by the number of occult LN metastases that are found after PLND and cystectomy in patients with MIBC. This percentage of occult LN metastases is highly dependent on

the primary tumour stage: 2-5% in ≤pT1, 8-18% in pT2 and 36-46% in ≥pT3 tumours[31-36]. Hypothetically the use of NIC reduces this percentage of occult LN metastases in patients with MIBC. To substantiate this hypothesis, the study in **chapter 6** was performed in which a consecutive series of clinically node negative (cN0) patients, who were treated with or without NIC were compared. These patients all underwent RC using the same PLND template during the study period. In the patients with locally advanced disease (cT3-4), the occurrence of LN metastases was significantly lower in the NIC group compared with the non-NIC group (21.9% versus 40.7%). This underlines the importance of NIC to erradicate occult micro-metastatic disease[37].

Despite several publications supporting this multimodality treatment approach with pre-operative chemotherapy, this treatment strategy has not been adopted as standard of care for non-organ confined bladder cancer [26,38-41]. According to a report from the National Cancer Data Base in 2007, peri-operative chemotherapy was administered to 11.6% of patients with stage III bladder cancer in the USA. Thus underlining the fact that perioperative chemotherapy is underused in stage III bladder cancer[42]. This is in concordance with a survey among Dutch urologists, in which was shown that only 25% of the respondents to the survey considered NIC for bladder cancer. Furthermore approximately 10% of eligible patients actually received neoadjuvant combination chemotherapy (personal correspondence with principal investigator dr J.L. Boormans). This may be due to the fact that many clinicians are reluctant to start NIC with respect to the potential toxicity it elicits. Ideally such toxic treatment would be started only in patients, who are likely to benefit, based on tumour characteristics. There have been varying reports on the use of molecular

markers to predict prognosis and chemosensitivity of bladder tumours. Especially the tumour suppressor proteins p53 and retinoblastoma (pRb) and their downstream effectors (e.g. p21) have been investigated in this respect[43-45]. The implementation of molecular markers may be the basis for indivualizing treatment for patients with non-organ confined bladder cancer [43,45]. Stadler et al. performed a phase III trial to evaluate chemosensitivity of patients with p53 inactivation determined by immunohistochemistry (IHC)[45]. Unfortunately this trial, randomizing patients with aberrant p53-IHC to 3 cycles of adjuvant MVAC versus observation, produced inconclusive results due to study limitations such as: high patient refusal rate, failure to receive assigned therapy and limited power of the study (due to better than expected overall patient outcome in case of aberrant p53-IHC). Such molecularly targeted therapy may require a combination of several molecular markers (e.g. p53, pRb, p21 and p27) in order to predict clinical outcome and response to treatment[44].

Cisplatin-unfit patients

When patients are unfit to receive cisplatin-based combination chemotherapy, they may be submitted to surgery immediately, as generally other regimens of induction chemotherapy (e.g. carboplatin-based treatment) are considered to be inferior compared to cisplatin-based treatment. However, as was described in **chapter 5**, carboplatin-based induction chemotherapy may prove to be a reasonable alternative for cisplatin-unfit patients with non-organ confined bladder cancer. The concerning study showed that induction treatment with gemcitabine and carboplatin for non-organ confined bladder cancer achieves comparable clinical and pathological response rates as well as survival outcomes to the cisplatin-based regimens[46].

Sequential chemoradiation for small cell carcinoma of the bladder

The bladder-sparing strategy, consisting of sequential chemoradiation (i.e. NIC followed by external beam radiotherapy), for patients with limited disease small cell carcinoma of the bladder (LD-SCCB), represents another multimodality treatment approach. The study that was reported in **chapter 8** concerning sequential chemoradiation in LD-SCCB, showed reasonable outcome results with a high bladder preservation rate (85.2%). Although the prognosis of patients with LD-SCCB treated with sequential chemoradiation remains poor, with a median DSS of 47 months and 5-years DSS 39.6% [47]. Because of experience with an increased risk for local toxicity in the bladder after concurrent chemoradiation, in our institution external beam radiotherapy is scheduled after the NIC. However, recently there have been reports on the beneficial effects of concurrent administration of radiosensitizing agents (e.g. cisplatin-based chemotherapy) potentiating the cytotoxic effect of radiotherapy [48]. As the techniques of external beam radiotherapy have evolved in recent years and the risks of local toxicity have been further reduced, the use of concurrent chemoradiation may be expected to gain terrain.

Notwithstanding these results, the optimal treatment strategy for these patients with LD-SCCB remains controversial, because of the low incidence of the disease. Some advocate NIC followed by radical surgery, with promising results [49]. To determine the optimal treatment approach for this rare and aggressive entity, a multi-center case-matched comparison between different treatment modalities (e.g. NIC with either surgery or radiotherapy) would be invaluable.

Conclusions

In conclusion, to improve the poor outcome of patients with high-risk bladder cancer:

- The multidisciplinary approach is essential

- More accurate clinical staging with novel imaging techniques is inevitable

- Molecularly targeted therapy will result in personalized cancer care

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