

SUMMARY

This thesis focused on two important aspects of MIBC; staging and treatment. **Chapter 1** is a general introduction in which the most important steps and time frames in bladder cancer research were discussed. Furthermore, an overview of the current knowledge of bladder cancer was presented. Then, we highlighted the knowledge gaps in the field of bladder cancer, which were addressed in the present thesis.

Part I

Part I of this theses focussed on the (incremental) value of PET/CT for staging MIBC. We evaluated two techniques to improve visualisation of primary bladder tumours by PET/CT. In **chapter 2**, a catheter-assisted protocol was applied. We found that flushing and subsequent retrograde filling of the bladder results in the highest rate of tumour visualisation and quantification. Flushing alone was inferior. In **chapter 3** delayed imaging after forced diuresis was evaluated and it was shown that delayed pelvic FDG-PET/CT imaging after forced diuresis detects more bladder tumours than standard FDG-PET/CT protocols. However, indeterminate bladder lesions on delayed PET/CT remain a problem and should be interpreted cautiously in order to avoid false positive results.

In **chapter 4** the clinical impact of PET/CT on bladder cancer patients was investigated. We showed that FDG-PET/CT provides important additional staging information, which influences treatment of MIBC in almost 20% of the patients. Patient selection for neoadjuvant chemotherapy was improved and futile attempts at curative treatment in patients found to have metastases were avoided. In **chapter 5** we evaluated whether the staging benefit of PET/CT was reflected in better prognostication of MIBC patients. The presence of extravesical FDG-avid lesions on PET/CT indeed was found to be an independent indicator of mortality and a better prognosticator than CT alone.

Then, in **chapter 6**, the use of PET/CT for evaluating response of bladder cancer patients with lymph node metastases, after neoadjuvant chemotherapy was elaborated. Although no definitive conclusions could be drawn from this small pilot study, our preliminary results suggested that PET/CT scanning appears feasible in evaluating nodal response to NAC and distinguishing between responders and non-responders.

Part II

Secondly, we evaluated different aspects of the treatment of patients with MIBC. Chapters 7 and 8 deal with two surgical treatment aspects. First, the long term functional and oncological results of the prostate sparing cystectomy (PSC) were described in **chapter 7**. Our long-

term data showed that, for a subset of carefully selected MIBC patients without evidence of urothelial carcinoma in the prostatic urethra/bladder neck and no prostate cancer, PSC is an oncologically safe procedure with excellent functional results.

The number of resected lymph nodes at the time of cystectomy is used as an important prognosticator, however this number is highly dependent on histopathological evaluation. In relation with two different pathology departments evaluation surgical specimens, the impact of the nodal yield on survival is described in **chapter 8**. Despite the statistically significant difference in lymph node yield in PLND specimens between both hospitals, this study revealed no significant differences in survival outcomes between both hospitals. Standardised histopathological methods should be agreed upon by pathologists before integrating nodal yield and subsequent lymph node density as indicators of the quality of surgery and as prognostic factors.

Chapters 9, 10 and 11 dealt with neoadjuvant-chemotherapy-related topics: In **chapter 9**, the question was addressed whether gemcitabine and carboplatin could be used as an alternative for patients who are unfit to received cisplatin-based neoadjuvant chemotherapy. Neoadjuvant gem/carbo for non-organ confined UC achieves comparable clinical and pathological response rates as well as survival outcomes to the CBCC schemes. Our data suggest that a carboplatin-based regimen can be considered a reasonable alternative for cisplatin unfit patients in the neoadjuvant setting. In **chapter 10**, the incidence of occult lymph node metastases after neoadjuvant chemotherapy and after direct radical cystectomy are compared in clinically node negative patients. These data suggest that, along with a downstaging effect on the primary bladder tumour, NAC is associated with a lower incidence of occult LN metastases at the time of RC. And in **chapter 11** the use of neoadjuvant chemotherapy for node positive bladder cancer patients is discussed. Prognosis for NPBC remains poor despite the use of induction chemotherapy. Nevertheless, in the present series, 1 out of 4 patients showed complete pathological response to induction chemotherapy with subsequently a significant CSS benefit (median CSS 127 months and 5-years CSS 63.5%). Clinical and pathological response to chemotherapy are predictive parameters for outcome.

Part III

The third part of this thesis contained a variety of bladder-cancer-related manuscripts. **Chapter 12** is an illustrative series of patients with severe complications after intravesical chemotherapeutic instillation, immediately after transurethral resection. It showed that extravasation can cause severe complications and diagnosis is often protracted. Considering the growing practice of immediate intravesical instillations, the number of patients with symptomatic extravasation is expected to rise. An increased awareness of this possible complication is warranted.

In **chapter 13**, we reviewed the role of biomarkers predicting response of non-muscle invasive bladder cancer on BCG induction, and of MIBC on neoadjuvant chemotherapy. Although there seems to be a potential for molecular biomarkers to predict the response to neoadjuvant therapies, to date, molecular markers have not conclusively proven to have additional value over the established clinicopathological variables and have not yet become part of (routine) clinical practice. **Chapter 14** is an addition to chapter 8.

Finally, in **chapter 15**, the results presented in thesis were discussed and suggestions for future perspectives were made.

All in all, it has become clear that MIBC no longer solely is the field of the urologist. A close cooperation between treating physicians (urologists, medical oncologists and radiation oncologists) and the supporting disciplines (pathologists, radiologists, and nuclear medicine physicians) is essential.