Chapter 10:
General Discussion and Future Perspectives

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Cystectomy is the still the standard treatment for invasive bladder cancer. The surgical management of bladder cancer has evolved in the past decades, with important improvements of perioperative care and techniques, and better insight in the importance of the extend of the accompanying lymph node dissection. The prognosis of bladder cancer and survival after cystectomy however improved only slightly, as the basic principles of cystoprostatectomy as treatment for bladder cancer have not changed. What did change in the past years is the increasing emphasis laid on quality of life issues after cancer surgery in addition to the oncological outcome, and the awareness that further improvement of cancer prognosis can be reached by improving the quality of the applied surgical procedures. This quality can not be taken for granted, but should be measured by registering and comparing treatment results.

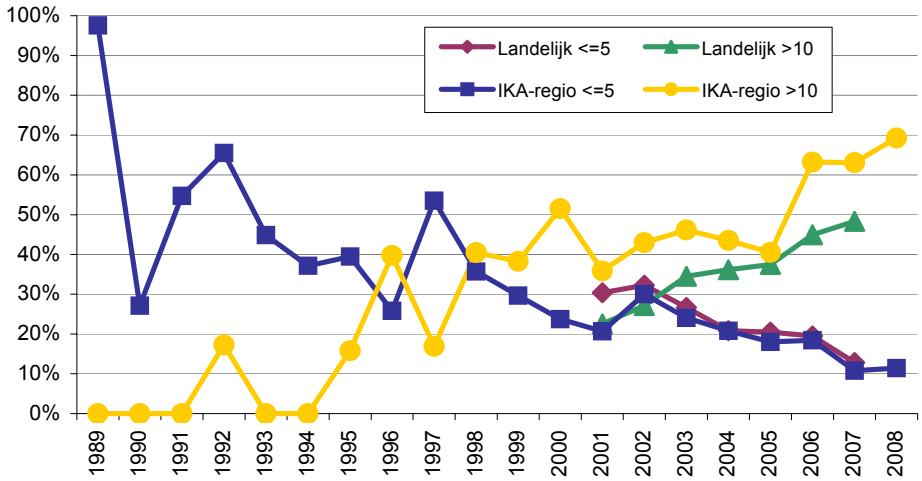
In **chapter two** we investigated in a population based setting the survival of bladder cancer patients and the local recurrence rate after cystectomy in the region of the Comprehensive Cancer Centre of Amsterdam. We chose to describe these two variables in order to estimate whether bladder cancer treatment in this region meets international standards. Survival is considered a solid end point, and in analogy to colorectal cancer we hypothesised that local recurrence in bladder cancer might be a good indicator of quality of surgery.[1-3] Local recurrence rates in oncological centres were lower but differences were not statistically significant compared to community hospitals. As the differences appear to be small in bladder cancer, much larger numbers of procedures have to be compared to find statistically significant differences. Procedural figures though are changing in the last years, with tendency of centralisation (figure 1).

In an ongoing analysis data from the whole of the Netherlands are collected, in which the number of procedures appears to be related to early treatment related death. These analyses may improve insight on the issue of hospital volume and oncological outcome in cystectomy. Growing evidence indicates that increased hospital volume improves cancer outcome, although it is difficult to define a minimum number of cystectomies. It is our personal opinion that in the case of cystectomy both hospital related factors as surgeon related factors are important in the prognosis of bladder cancer. Minimal case loads of 6 and 11 cystectomies per year have been mentioned, but hospitals performing over 50 cystectomies per year still have superior mortality rates compared to smaller (10 cystectomies or less) institutions. Regardless of the threshold that will be chosen, centralization of bladder cancer treatment will lead to improved cancer care. Not only because of the "practice makes perfect" principle, but literature also shows that specialised (semi)academic centres have more often the disposal of more technical and personal resources.[4-7]

In colorectal cancer local recurrence rates were found to be dependent on both the skills and experience of the individual surgeon as on hospital related factors.[8-10] But comparison of local recurrence rates after cystectomy has its limitations. Between large cystectomy series in literature no uniform definition of a local recurrence, nor identical follow-up schedules are used. Local recurrence rates are probably under-reported as the finding of distant metastases decreases

the need for intensified local follow-up. As a result higher local recurrence rates can reflect both inferior quality of cystectomy and superior quality of follow-up. If local recurrence rates are to be used as a mean to compare quality of cystectomies, the application of uniform definitions, follow-up schedules and calculation methods is essential.

Figure 1: *The percentage of cystectomies per year performed according to hospital volume.*



Source: O. Visser ; comprehensive cancer centre Amsterdam

The registration (and comparison) of treatment results are more and more used in public debates to determine the quality of care in regional and economical contexts, although quality of care is extremely complex as many mutually dependent factors play a role. In the near future these subjects will be important for patients, insurance companies and referring doctors in their choice for treatment centres. The primary goal of registering and comparing treatment results though is to enlarge skills and improve the applied treatments by internal feedback and increased transparency.

Staging the disease according to TNM classification plays a key role in therapeutic strategy and prognosis. Lymph node metastases are the most important prognostic variable in determining the outcome after cystectomy. At present, there is no reliable non invasive tool to determine whether lymph node metastases are present. Imaging modalities such as ultra small super paramagnetic particles of iron oxide (USPIO) and diffusion weighted magnetic resonance imaging (DW-MRI) are promising, but are difficult to interpret and reported results are inconsistent. Imaging techniques develop fast with increasing computed capacities and the combination of the above named, USPIO-DW-MRI, is promising, but is not yet available as a general diagnostic tool.[11] However, improved accuracy of diagnosing lymph node metastases will present another dilemma; what is the best treatment strategy for these patients? Until now

cisplatin based chemotherapy is the only treatment providing the potential of long-term progression free survival in metastasized bladder cancer, and has shown to be more effective in patients with nodal metastases compared to visceral metastases.[12,13] Whether lymph node positive patients should be treated with neo-adjuvant chemotherapy and surgery based on response, with immediate adjuvant chemotherapy, or with deferred (adjuvant) chemotherapy in case of relapse of disease after cystectomy with extended lymph node dissection is still unclear.

Neo-adjuvant chemotherapy provides two potential advantages; early treatment of occult metastases and the option of treating these patients according to response of disease with "in vivo" assessment of chemo-sensitivity. Remission after chemotherapy is a powerful prognostic factor. Non-responders may be spared major local surgery which will not improve their prognosis. Response was the most powerful variable in patients treated with neo-adjuvant MVAC as described in **chapter 3**, and these data suggest that lymph node status after chemotherapy is more important than local tumour status in this aspect. It is hard to explain the difference of response of tumour cells in lymph nodes and at the primary site. The (partial) lymph node dissection prior to chemotherapy may play a role, or there may have been large differences between tumour load in lymph nodes and tumour load at the primary site. Patients with post-MVAC positive nodes may have had a greater burden of metastatic disease prior to treatment as well, but it is reasonable to assume that the benefit of chemo-therapy on occult visceral metastases is negligible in the absence of a lymph node response. A complete response after chemotherapy is evidently associated with improved prognosis, but the difficulty is in identifying those patients with a good prognosis after a partial response and to determine their subsequent treatment. These data suggest that patients without evidence of lymph node metastases after chemotherapy and at least a partial response of the primary site are good candidates for cystectomy.

The down-site of neoadjuvant chemotherapy is that definite local treatment is postponed, not only by the time needed to administer chemotherapy, but also by the time to recover from chemotherapeutic side effects. Postponing surgery might have an adverse effect on survival, especially in the light of the increased emphasis on the therapeutic role of lymph node dissection, which can be curative in itself.[14-20]

Studies evaluating adjuvant chemotherapy have been limited by inadequate statistical power so far. However, randomised clinical trials suggest a modest survival benefit for neoadjuvant Cisplatin based chemotherapy in high risk patients, but it is important to realise that many patients included in these trials were clinically N0/Nx-M0-patients.[21] The standard use of neoadjuvant chemotherapy in N0/Nx invasive bladder cancer might accelerate the development of novel agents, as the availability of tumour tissue before and after chemotherapy can provide in determining molecular and biological characteristics predictive for response. It is however not routinely used in the Netherlands for localised diseases, as the evidence for neoadjuvant chemotherapy in localised bladder cancer is small. Sub-analyses suggest a more substantial benefit for patients with high risk disease.[22] At present, lymph node

positive patients should be treated preferably in randomised trials. In the absence of randomised trials the treatment at present is neo-adjuvant Cisplatin based chemotherapy and subsequent local treatment in case of (partial) response. The standard regimen should be HD-MVAC (as HD-MVAC is associated with improved survival, faster delivery and less toxicity as compared to classic MVAC) while gemcitabine plus cisplatin (which is less toxic and achieves similar response rates, but is less extensively tested in a neo-adjuvant setting) might be an alternative.[23-26]

Apart from stage and grade the histological subtype is important in defining the definite treatment strategy. Small cell carcinoma (also referred to as oat-cell carcinoma or small-cell neuroendocrine carcinoma) is a distinct histological entity, with an origin from a multipotential stem cell which has the ability to differentiate in a range of tissue types.[27] It is characterised by an aggressive clinical course with early metastasised spread and dismal prognosis. Prognosis is mainly influenced by the extent of disease at diagnosis and the use of chemotherapy, similar to its more common pulmonary equivalent. Because of the relative rarity in the bladder no randomised trials exist, and as a result there is no standard treatment for this tumour. The role of chemotherapy in small cell lung cancer is well established, and data described in **chapter 4** and literature confirm an important role for (neoadjuvant) chemotherapy in small cell bladder cancer as well.[28,29]

Small volume disease limited to the bladder might be treated by cystectomy alone, although staging small cell bladder cancer according to the TNM classification appears to fail as tumour stage is often not independently associated with survival, suggesting that micrometastases are present even in clinically localised disease.[30] In small cell lung cancer the clinical utility of a two-stage system has been supported by multiple studies. Because of the clinicopathological similarities between both tumour sites, the simplicity of the two-stage system and its clinical relevance for treatment decisions, we defined limited- and extensive disease in analogy to small cell lung cancer. This treatment algorithm as described in chapter 4 appeared to be feasible and provides in a uniform strategy for this rare disease, although performance status precludes chemoradiation in a significant proportion of the patients with limited disease. The fact that none of the patients died of locoregional tumour progression supports our view that a bladder-preserving strategy in limited disease is an attractive concept, taking into account that prognosis is mainly determined by the extent of the disease and the use of chemotherapy.

Radical cystoprostatectomy is the standard treatment for invasive localized transitional cell cancer of the bladder, and remains the standard by which new treatments are judged. The basic oncological principles in cystectomy included wide surgical margins where possible and the avoidance of tumour spill as described in the 1940's and 50's by Marshall and Whitmore.[31] The side effects of radical cystectomy however are substantial, and side effects of the urinary diversion and an impaired sexual response and urinary sphincter function (in case of orthotopic neobladders) importantly determine quality of life after cystoprostatectomy.[32-34] Over the past decades the preservation of organ function coupled with local cancer control gained interest again in urology, with

treatment strategies aiming at bladder preservation or nerve sparing techniques. In order to be a reasonable alternative for cystectomy, bladder preservation has to meet the following standards: it should preserve a well functioning bladder, prevent local failure and distant metastases, and provide equivalent survival. Crucial hereafter is a close surveillance for bladder recurrences with the option of salvage cystectomy, preferably with preservation of the different urinary diversion options.

Most schemes combine maximal transurethral resection with (neo)adjuvant chemotherapy or radiation therapy with concurrent radiation sensitizing chemotherapy.[35-38] Brachytherapy as described in **chapter 5** is a less well known bladder preserving strategy for selected patients. Despite high local control rates of 70-90% and excellent maintenance of bladder function reported in multiple series, brachytherapy is not generally accepted as a reasonable alternative for cystectomy.[39-42] The most important reason is the fear that bladder sparing strategies lead to inferior local results and decreased survival, and attempts to prove otherwise by randomised trials comparing these modalities have failed so far. Notwithstanding the limitations of a non-randomized comparison of two different treatment forms, the analysis of chapter 5 suggests that bladder preservation with brachytherapy does not compromise survival. A major issue in the discussion regarding brachytherapy is whether the good results are a direct result of patient selection. Meticulous patient selection however must play a key role in identifying those patients candidate for bladder preservation. Whether local control is achieved by TUR, partial cystectomy, radiation or a combination remains unknown in the absence of prospective comparative trials. Although the different nature of the two treatment modalities makes a traditional randomized trial very challenging, bladder sparing approaches will only gain popularity if the above named standards are demonstrated in well designed prospective trials of equivalence.

The option of salvage cystectomy with any known type of urinary diversion in case of local failure after bladder preservation is feasible with acceptable morbidity, both after interstitial radiotherapy and external beam radiotherapy as described in **chapter 6.** A highly significant factor for adverse outcome and death from local tumour-recurrence was incomplete resection. Consequently salvage cystectomy should only be attempted if complete resection is probable. Clinical understaging after radiotherapy though is common, and improvement of preoperative selection is needed.

The wide margins of cystectomy as described by Marshall and Whitmore narrowed with the introduction of nerve sparing techniques. Walsh described the anatomy of the pelvic innervation and showed how the neurovascular bundles containing cavernous nerves can be preserved during prostatectomy for prostate cancer.[43] In a similar way the nerve sparing cystoprostatectomy was developed. Nerve sparing procedures require dissection closer to bladder base and prostate, but are considered oncologically safe with improved postoperative sexual functions and urinary continence of orthotopic neobladders.[44-48] Sparing of the seminal vesicles and prostate capsule might further reduce the risk of damaging the plexus pelvis and neurovascular bundle, together with its blood supply. The results of this prostate sparing cystectomy,

which is arguably one of the most discussed topics in the field of urology today, are described in **chapter 7**. Arguments against prostate sparing procedures are based on the risk of late development of prostate cancer, the risk of prostatic involvement with transitional cell cancer, and on the potential risk of local recurrence of the bladder tumour. There is little discussion about the functional results after prostate sparing cystectomy, which are generally considered better than after nerve sparing cystectomy.

With concern to the development of prostate cancer, it is recognized that de prevalence of prostate cancer exceeds that of clinically detected cancers. It has been hypothesised that prostate cancer prevalence is higher in patients with bladder cancer due to a common pathway of carcinogenesis.[49] The overall reported incidence of prostate cancer in cystoprostatectomy specimens varies between 14 and 48%.[50-53] The relationship between clinically and incidentally detected cancer however is uncertain, with proportions of clinically insignificant prostate cancers varying between 30% to 80%.[51,53,54] Furthermore there is the concern of prostate involvement with transitional cell cancer, with incidences of prostatic TCC between 12% and 48%.[55,56] All of the above named percentages though apply to an unselected group of patients. Patients scheduled for prostate sparing cystectomy have a thorough pre-operative work-up to exclude prostatic involvement, which makes this group of patients a highly selected group. As a consequence, these percentages are likely to drop dramatically. Local recurrence rates and survival as described in chapter 7 are comparable with contemporary cystoprostatectomy series, and subsequent prostate cancer was detected in only 3% after prostate sparing cystectomy. These figures do not differ from most prostate sparing cystectomy series.[57-60] Prostate sparing cystectomy should not be regarded as a standard procedure, but until now we consider this procedure oncologically safe in meticulously selected and well informed, highly motivated patients. Ultimately, the oncological equivalence or non-inferiority of bladder sparing strategies and prostate sparing cystectomy will require prospective trials of equivalence.

Chapter 8 describes the complications and functional results of the four most commonly used urinary diversions after cystectomy in The AvL /NKI, including neobladder after prostate sparing cystectomy. These data demonstrate again that cystectomy with any subsequent diversion remains a procedure with considerable morbidity. We found no evidence that age, ASA-score, positive lymph nodes, extravesical tumour growth, or previous radiotherapy are contraindications per se for any diversion. In the last decade there has been a shift from the initial oncological care with upper urinary tract protection to an increasing relevance of quality of life, reflected in the fact that orthotopic diversions account for almost half of the used urinary diversions at present.[61] Functional results of an orthotopic diversion were good in our series, but at the cost of more late complications compared with cutaneous diversions. These patients should further be informed about the probability of nightly incontinence and need of self catheterisation for post void residual urine. There is however no superior type of diversion, and most studies on quality of life show equally good overall quality of life irrespective of the chosen urinary diversion.[62,63] In the absence of a superior diversion, patients should choose their preferred diversion

with realistic expectations based on thorough pre-operative consultation by multidisciplinary teams.

Laparoscopic (open assisted) cystectomy is developing fast, and may offer patients the potential of reduced blood loss, decreased morbidity and quicker recuperation. Although intracorporeal construction of the urinary diversion and the extended lymph node dissection still pose major technical challenges, the open assisted approach will be further developed, investigated and incorporated in the near future.

Roughly 50% of the patients treated by cystectomy develops a recurrence of disease. The follow-up schedule as described in **Chapter 9** focuses on timing and patterns of recurrence of the primary bladder tumour. Patients who developed a recurrence in the remaining urinary tract were excluded, as these tumours should probably be regarded as new primaries, not as metastases from the original tumour. Furthermore it does not provide follow-up of functional and metabolic complications from the used diversion. Our data suggest that a risk adjusted follow-up schedule should be applied. Risk calculation is importantly based on stage, as suggested by Kuroda and Bochner et al, but can be further refined by other prognostic factors such as tumour positive margins and pre-operative dilatation of the urinary tract.[64,65] Supplementary division beyond the histological classification of bladder cancer into clinical relevant molecular subgroups by biomarkers and genetic profiles are being tested, which might add in further refinement of risk calculation of recurrence and the identification of those patients who might benefit from subsequent treatment.[66] As cost-benefit analyses will become more and more important with increasing age and the growing incidence of cancer, risk adjusted follow-up schedules might reduce costs while still identifying those patients at risk of recurrence.[67] Above this, we should realise that at present the success of recurrence treatment is limited, and cure rates are low.

Concluding Remarks

This thesis evaluates the treatment results, side effects and follow-up of different treatment strategies for invasive bladder cancer. Cystectomy remains the corner stone of therapy, but innovative techniques focusing on improved functional outcome or bladder sparing appear reasonable alternatives in selected patients. Uniform definitions of follow-up and complication registration are needed to compare outcomes among institutions, individual surgeons, and treatment strategies. Our daily practice in the treatment of bladder cancer should increasingly take place in prospective clinical trials of equivalence for those patients candidate for disparate treatment strategies, in order to make them more widely accepted. The presented studies should encourage informed discussion on dissimilar treatment modalities, which can be beneficial in defining clinical trials and guiding urologists and patients in the difficult choices confronted with after the diagnosis of invasive bladder cancer.

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