Summary

A short overview of the etiology, diagnosis, treatment, and prognosis of bladder cancer is given in chapter 1. Chapter 2 describes the incidence and survival data of bladder cancer between 1989 and 2009 in the Netherlands. For both males and females the incidence of non invasive bladder cancer increased, the incidence of invasive bladder remained the same in males and slightly increased in females. Reasons for this might be the increased awareness of both patients and urologists of signs and symptoms of early bladder cancer. The number of cystectomies in stage II and III bladder cancer patients is still rising for both patients below and above the age of 75. So far survival did not improve.

Identifying the patients in whom non-muscle invasive bladder cancer (NMIBC) will progress despite bladder sparing therapy is a major challenge. In chapter 3 we described a group of patients presenting with NMIBC that progressed to muscle invasive disease and compared survival in patients with patients presenting with primary muscle invasive bladder cancer, all treated by cystectomy and regional lymph node dissection. Survival in patients who progress to muscle invasion is not any better than patients presenting with primary muscle infiltrating cancer. Patients with high-risk NMIBC who progress to muscle invasive disease before cystectomy have even a worse prognosis compared to patients with low-intermediate risk NMIBC who progress to muscle invasion. The number of patients with locally advanced and lymph node positive disease was unexpectedly high in the group that progressed to muscle invasive disease. The optimal timing of cystectomy is difficult to determine, active restaging (re-TUR) during conservative management of non muscle invasive bladder cancer and the use of EORTC tables can be helpful. T-stage and grade progression are probably just as important signs for early cystectomy as the traditional criterion of muscle invasion.

Chapter 4 describes a small group of bladder cancer patients presenting with supra-regional lymph node metastases without synchronous hematogenic metastases treated with combination therapy. When patients achieve a clinical complete or partial response after chemotherapy, cystectomy follows. In this selected group 24% of patients survive 5 years after cystectomy. In Chapter 5 we retrospectively evaluate the clinical and oncological outcome in a series of 16 patients with limited-disease small cell carcinoma of the bladder (LD-SCCB), who were treated with sequential chemoradiation. Due to poor prognosis because of early hematogenic spread a bladder-preserving strategy with sequential chemoradiation is an attractive concept in contrast to focus on local control by cystectomy. Long-term remission and potentially cure can be achieved in some, with 2 of the patients (11.7%) in this series still free of disease after more than 5 years at a local recurrence rate of 23.5%. The fact that none of the patients died of locoregional tumour
progression supports our view that cystectomy is not the preferred initial treatment for LD-SCCB. **Chapter 6** deals with the association of clinical factors, complications and functional results of 4 different diversions after cystectomy. In total 281 patients underwent a cystectomy and urinary deviation: Of these patients 118 received an ileal conduit (IC), 51 an Indiana pouch (IP), 62 a neobladder (CN), and 50 a sexuality preserving cystectomy and neobladder (SPCN). 124 patients developed one or multiple complications within the first 30 days, leading to an early complication rate of 44%. High ASA-score was the only factor significantly associated with early major complications in both univariate (ASA 1 vs. 3: HR 0.32; 95%C.I. 0.14-0.72) and multivariate analyses (HR 0.36; 95%C.I. 0.14-0.91). None of the other variables were associated with early major or minor complications. Late complications occurred in 139 patients (51%). Patients with an ileal diversion had lower risk of developing late complications compared to patients with a neobladder; 49%(IC), 62%(IP), 59%(CN), 60%(SPCN), respectively. Provided that patients’ choice is based on thorough pre-operative consultation, we found no evidence that age, ASA-score, positive lymph nodes, extravesical tumour growth, or previous radiotherapy are contraindications per se for any diversion.

Organ preservation has been a major goal in modern oncological treatment strategies. For many other types of malignancies such as: breast cancer, head- and neck cancer, rectal cancer and soft tissue sarcomas of the limbs conservative treatment with preservation of function is standard care. However, for patients with muscle-invasive bladder cancer radical cystoprostatectomy, with or without chemotherapy, is still considered standard treatment. In **Chapter 7** the long term oncological results of the prostate sparing cystectomy (PSC) are presented. Goal of this procedure is to preserve sexual functions without jeopardizing oncological outcome. A selected group of 63 men underwent a PSC, and were matched with 73 men who received a standard cystectomy and orthotopic neobladder. No statistically significant differences were found in local recurrence rate or distant metastases (7.9% and 16%, p=0.1; 29% and 33%, p=0.4 in the PSC and in the SC, respectively). The 3 and 5-year disease specific survival rates were 77% and 66% in the PSC group and 68% and 64% in the SC group (log-rank, p=0.6). In the multivariate analysis, only extravesical disease (HR 3.58, p=0.003) and tumour positive lymph nodes (HR 5.75, p=0.0004) were significantly associated with survival. Two patients in the PSC group developed prostate cancer, one died after 126 months due to metastatic bladder cancer; the other is still alive at 50 months of follow-up. In the SC group, incidental prostate cancer was found in nine patients (18%). None of the local recurrences in the PSC group was in the remnant prostatic urethra or prostate.

After cystectomy pelvic recurrence rates vary between 4-34%, while distant metastases occur in up to 50% of all patients, both highly dependent on stage. In **Chapter 8** we
analysed patterns of recurrence and relapse presentation in association with clinicopathological factors, and the tools used for diagnosis. We studied 343 consecutive patients treated with cystectomy and bilateral lymphadenectomy for bladder cancer at the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital from 1990 till 2005. Pelvic recurrences were more often seen with increasing pathological T-stage and after non-radical procedures. Sexuality preserving procedures were associated with less pelvic recurrences. Only pT4b tumours were independently associated with pelvic recurrence in multivariate analyses. In multivariate analyses tumour positive lymph nodes, and pre-operative dilatation of the upper urinary tract remained independent risk factors for development of distant recurrences. 84% of all recurrences occurred within 2 years, the latest recurrence was detected 7.9 years after cystectomy. Of all recurrences 64% was symptomatic at the time of diagnosis, while the minority (34%) was diagnosed at the standard follow-up. Follow-up after cystectomy should be based on risk adjusted schedules. Although the majority of recurrences presents with symptoms, these data show a survival benefit after a-symptomatic recurrence. High pathological T-stage, tumour positive lymph nodes, pre-operative dilatation of the upper urinary tract, and tumour positive surgical margins are clinicopathological factors that can help selecting patients at high and low risk for recurrence, resulting in less frequent and more cost-effective follow-up. For now, therapeutic options in patients with symptoms at time of recurrence are limited and prognosis is poor.

In Chapter 9 the outcome after treatment of bladder cancer is compared between low volume hospitals and an oncology centre (NKI-AVL) in the Greater Amsterdam Region(CCCA). All primary bladder tumours diagnosed and treated during 1989-2003 were selected from the CCCA Registry, a population based cancer registry with complete regional coverage (population 3.0 million). A total of 1185 cystectomies were performed in the twenty hospitals of the CCCA region. The postoperative mortality (≤ 30 days after cystectomy) for all hospitals combined was 3.2%, but ranged from 0% to almost 10%. Between 1989-2003 the postoperative mortality was 1.8% at the oncology centre compared to 3.5% in all other hospitals combined. 184 patients (19.9%) developed a locoregional recurrence after cystectomy, including six more than five years after cystectomy. The vast majority (91%) of recurrences occurred within three years after cystectomy, 81% within two years. No statistically significant difference in locoregional recurrence rate was observed between the oncology centre (18.9%) and all other hospitals combined (20%). More procedures have to be compared to refute or prove the benefits of centralization. In Chapter 10 the short term outcome of cystectomy patients is described comparing two different perioperative protocols. Between June 2007 and November 2008, 85 consecutive patients with bladder cancer were treated with cystectomy and urinary diversion. Patients were operated in 2 hospitals by 4 experienced
urologic surgeons. In hospital A patients were enterally fed via a postpyloric tube while the nasogastric tube (NGT) was removed within 24 hrs after cystectomy and selective bowel decontamination was given until normal oral intake. In hospital B post cystectomy management consisted of total parenteral nutrition (TPN) by a central venous line and NGT removal after 24hrs. Hospital stay and complications were compared between the two hospitals. More than half of all patients (52%) developed one or more complications within 30 days after surgery, 37% in hospital A and 71% in hospital B. Patients treated in hospital A had a shorter length of stay 13 days vs. 19 days, as compared to hospital B patients. Enteral nutrition might be advantageous as compared to parenteral nutrition showing fewer complications and shorter hospital stay. Selective bowel decontamination may have an additional role in preventing infectious complications after cystectomy.

Intra peritoneal spread of bladder cancer is a rare event in contrast to advanced ovarian, colon, gastric, pancreatic, and breast cancer. In Chapter 11 we describe a 45-year old female patient with a 20-year history of recurrent non-muscle invasive bladder cancer treated with BCG instillations and repeat transurethral resections and eventually a cystectomy and nefro-ureterectomy. This patient with a very long history of bladder cancer presented with clinical signs and pre-operative imaging of ovarian cancer four years after cystectomy, however pathological examination revealed extensive peritoneal dissemination from transitional cell carcinoma (TCC) of the bladder. The seeding potential of high-grade TCC is well known and illustrated by recent reports of port site metastases after laparoscopic surgery.\textsuperscript{1-3} Although the exact mechanism is not completely clear in this patient, this case most probably underscores the seeding potential of transitional cell carcinoma.