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Influence of Body Mass Index on Operability, Morbidity and Disease Outcome after Radical Cystectomy

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Dedicated to my husband Tobias and my two sons Joshua and Kilian

Abbreviations:

ACS	American Cancer Society
AICR	Association for International Cancer Research
AJCC	American Joint Committee on Cancer
BCG	Bacillus Calmette-Guérin
BMI	body mass index
BTA	bladder tumor associated antigen
BTA TRAK	test for measuring human Complement Factor H antigen in urine
CDC	Centers for Disease Control and prevention
cdk2	cyclin-dependent kinase 2
CT	computer tomography
DNA	desoxyribonucleic acid
EK	erythrocyte concentrate
FANFT	N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide
G	grading
kg/m^2	kilograms/meters squared
M	metastasis
Max	maximum
min	minutes
Min	minimum
MONICA	Multinational MONItoring of trends and determinants in Cardiovascular disease
MRI	magnet resonance imaging
M-VAC	methotrexate, vinblastine, doxorubicin, and cisplatin
n	number
N	lymph node

Na^+/H^+	sodium/hydrogen ion
NMP22	nuclear matrix protein 22
p21	protein 21 (cyclin-dependent kinase inhibitor)
p53	protein 53 (tumor suppressor gene)
R	resection or surgical margins
SD	standard deviation
SEER	Surveillance Epidemiology and End Results
SPSS	Statistical Package for the Social Sciences
T	tumor
TNM	tumor, lymph node, metastasis
TUR	transurethral resection
TURB	transurethral resection of the bladder
UICC	Union Internationale Centre le Cancer
WHO	World Health Organization

Contents

1 Introduction

1.1 Epidemiology and etiology

Bladder cancer accounts for 3% of all malignant tumors [Tanagho and McAninch 2000]. It is the fourth most commonly diagnosed cancer in men and the ninth in women [Lerner 2005]. A male-to-female ratio of 2.7-to-1 and a tendency towards the Caucasian race is known to exist. Bladder cancer is also the second most prevalent cancer of the genitourinary tract. Depending on the source, the age of diagnosis lies between the ages 65 to 70 and older [Calatayud Sarthou, et al. 1994, Tanagho and McAninch 2000]. Lerner et al. estimated a worldwide 5-year prevalence of over 1,000,000 in the year 2004. In Germany, the prevalence is estimated at 16,000 yearly [Lerner 2005, München 2003]. At time of diagnosis, the patients show 70% to 80% superficial bladder tumors [Society 2005] and 15% have metastases to the regional lymph nodes or distant regions [Tanagho and McAninch 2000].

Cigarette smoking is responsible for 50-80% of cases in men and women [München 2003]. The risk is dependent on dosage, duration and vocational exposure [Abu-Abid, et al. 2002, Thompson 1990]. The determining factors in causing bladder cancer are nitrosamine, alpha- and beta-naphthylamine, which smokers excrete in their urine [Tanagho and McAninch 2000].

The carcinogens of bladder cancer have been classified into four groups, which include cigarette smoking, aromatic amines, drugs and chronic urinary tract infections [Helpap and Kollermann 2000]. A latency period of 10 to 40 years is usually required before the bladder cancer promoters cause the malignant transformation of normal cells [München 2003].

Aromatic amines are absorbed through the gastrointestinal tract, lungs and skin [Rübben 2001]. The inactivation of aromatic amines occurs in the liver by the enzyme N-acetyl-transferase; therefore, the population with “slow-working” N-acetyl-transferase are also at higher risk in developing bladder cancer [München 2003].

Employees in the “chemical, dye, rubber, petroleum, leather and printing industries” are at higher risk for bladder cancer, due to the contact with explicit vocational carcinogens such as 2-beta-naphythylamin, benzidine, 4-amino-biphenyl and aniline [München 2003, Tanagho and McAninch 2000]. This population accounts for 15-35% of cases, mostly in men [Matanoski and Elliott 1981].

The drugs chlornaphazine, phenacetine and cyclophosphamide play a significant role in the malignant transformation of epithelial cells in the bladder. Chlornaphazine, whose structure resembles that of 2-beta-naphythylamin, was used as a treatment for polycythaemia up into the year 1963 [Rübben 2001]. Phenacetine not only causes interstitial nephritis, but is also responsible for urothelial cancer in the upper genitourinary tract. Gonwa et al. reported that 5-10% of phenacetine-induced interstitial nephritis patients developed urothelial cancer in the renal pelvis and ureters [Gonwa, et al. 1980]. The active metabolite structure of phenacetine also resembles that of an aromatic amine [Rübben 2001]. Cyclophosphamide-induced cystitis also increases the risk of bladder cancer development [Fairchild, et al. 1979]. Due to the implementation of 2-mercaptoethane sodium sulfonate (Mesna) as a cystitis prophylaxis, this risk can possibly be disregarded [Rübben 2001].

Chronic urinary tract infections, through continuous urethral catheter usage, is often associated with squamous cell cancers of the bladder [Warren 1987]. Bilharzial infections by *Schistosoma haemotobium* are responsible for 60% of bladder carcinomas diagnosed in Egypt, parts of Africa and the Middle East [El-Bolkainy, et al. 1981]. Other factors associated with bladder cancer are bladder stones and physical trauma [Hicks 1982, München 2003].

1.2 Pathogenesis

The transformation from a normal urothelial cell into a malignant cell is an aspect involving many genetic events. Considering that the p53 mutation frequently arises in colon and bladder cancers [Miyao, et al. 1993, Sidransky, et al. 1991], it can be assumed that this nuclear phosphoprotein plays a significant role in the malignant transformation of normal urothelial cells.

When a point mutation or gene deletion takes place along chromosome 17, this “universal sensor of genotoxic stress” loses its ability to stimulate the production of p21 protein, which binds to cdk2, a cell division-stimulating protein, thus causing a termination in the cell division (provided by Andrea Ladd, former HHMI predoctoral fellow, Baylor College of Medicine, Houston) [Greenblatt, et al. 1994, Harris 1996, Ko and Prives 1996, Levine 1997].

Urothelial hyperplasia, a proliferation in the number of cells, marks the beginning of neoplastic alteration in urothelial cells of the bladder in Fischer rats after the animals were fed N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT) [Friedell, et al. 1977]. The hyperplasia of the urinary bladder was also found to be irreversible. While the animal model goes through the following stages (hyperplasia→metaplastic changes→cancer), the human tumors can arise from normal, hyperplastic or metaplastic cells [Tanagho and McAninch 2000].

A three-step theory to tumor progression has been proposed by Liotta, 1986 [Liotta and Rao 1986]. The first step involves the attachment of tumor laminin receptors to the basal membrane of urothelial cells. These laminin receptors come in great numbers along the periphery of invasive tumor cells [Wewer, et al. 1986]. Proteases, such as type IV collagenase are produced, resulting in the disintegration of the basal membrane. With the secretion of cytokines, cell motility is activated and the initiation of tumor progression is completed.

1.3 Histopathology

There are benign and malignant tumors found in the bladder. Malignant epithelial tumors of the bladder encompass up to 98% of all bladder cancers [Tanagho and McAninch 2000]. The majority of these epithelial tumors, about 90%, are classified under transitional cell carcinomas. They appear mainly as papillary and exophytic lesions [Tanagho and McAninch 2000]. Papillomas answer for 2% of all transitional cell carcinomas [Friedell, et al. 1977], and according to the World Health Organization, papillomas are defined as papillary tumors with a top layer of normal transitional cells. Papillomas are

uncommon and in about 16% progress to higher grade tumors [Lerman, et al. 1970].

Carcinoma in situ is defined as a non-papillary, noninvasive and anaplastic intraepithelial disease [Otto and Rubben 1991]. It can appear as a primary tumor without any association with a papillary tumor, or as a secondary tumor in affiliation with a papillary tumor [Otto and Rubben 1991]. Otto, 1991 estimates the rate of tumor progression from a carcinoma in situ into a low-differentiated invasive bladder cancer at around 83%.

The nontransitional cell carcinomas include adeno-, squamous cell, undifferentiated and mixed carcinomas [Tanagho and McAninch 2000]. Adenocarcinomas account for 2% of all bladder cancers and muscle invasion is often present at time of diagnosis. Squamous cell carcinomas account for approximately 10% of all bladder cancers and often coincide with chronic bladder infections. Undifferentiated and mixed carcinomas are rare and account for 2-6% of all bladder cancers.

Secondary bladder tumors caused by infiltration from tumors in the adjoining organs, such as the prostate gland and colon, and metastases from melanomas, breast, gastric and lung cancer are rare [München 2003].

1.4 Staging and classification

The AJCC (American Joint Committee on Cancer)/UICC (Union Internationale Centre le Cancer) proposed its first TNM classification for malignant tumors in 1987, allowing a description of the primary tumor, the status of the lymph nodes and the location of cancer metastasis. This TNM classification has been internationally acknowledged and undergoes remodeling every few years. The last modification took place in 2002 and has been summarized in the tables below.

Primary Tumor	
Tx	Primary tumor not assessable
T0	No confirmation of primary tumor

Tis	Carcinoma in situ
Ta	Noninvasive papillary carcinoma
T1	Subepithelial infiltration of tissue (Lamina propria)
T2	Infiltration of muscle tissue
T2a	Infiltration of superficial muscle tissue
T2b	Infiltration of deeper muscle tissue
T3	Infiltration of perivesical tissue
T3a	Microscopically
T3b	Macroscopically
T4	Infiltration of the prostate gland or uterus, vagina, pelvic or abdominal wall
T4a	Infiltration of the prostate gland, uterus or vagina
T4b	Infiltration of pelvic and abdominal wall

Lymph Nodes	
Nx	Status unknown
N0	No regional lymph node metastasis
N1	Metastasis in one lymph node with diameter of ≤ 2 cm
N2	Metastasis in one lymph node with diameter of 2-5 cm or many lymph nodes with diameter of ≤ 5 cm
N3	Metastasis in a lymph node with diameter > 5 cm

Distant Metastasis	
Mx	Distant metastasis not assessable
M0	No distant metastasis
M1	Distant metastasis confirmed

In order to communicate internationally and encourage an exchange of statistical information, the WHO (World Health Organization) created a histological classification of urinary bladder tumors [Sobin 1978]. The foundation of this classification is based on constitution of the urothelium, cell size, urothelial lesions with cellular atypia, neoplasms of noninvasive papillary and invasive tumors [Mostofi FK 1999]. The latest revision of the WHO classification occurred in 2004, but has not yet been validated. The table below exhibits the WHO classification with 3 grades.

Grading	
G1	Well-differentiated papillary tumors; limited atypia and mitoses
G2	Moderate increase in atypia and mitoses
G3	Cell layer and cell size expansion; noticeable pleomorphism and mitoses

The above mentioned TNM classification criteria plus the depth of tumor infiltration into the bladder wall, tumor differentiation and hydronephrosis constitute the main prognostic factors in bladder carcinomas [Rübben 2001, Skinner 1977]. The incidence of death from bladder cancer correlates with the grade of the diagnosis.

1.5 Superficial vs. invasive bladder carcinoma

1.5.1 Superficial bladder carcinoma

The superficial bladder carcinoma is defined by the following TNM classifications: Tis, Ta and T1. They account for 80% of all newly diagnosed bladder cancers and are mostly well differentiated [Prout, et al. 1979]. The superficial, noninvasive and well differentiated bladder carcinomas can often be cured by transurethral resection (TUR) with or without intravesical chemotherapy, such as valrubicin, thiotepa, mitomycin, and doxorubicin [http://www.urologychannel.com/bladdercancer/treatment.shtml]. The recur-

rence risk for bladder cancer following 20 years or until death after the initial resection remains at about 80% [Holmang, et al. 1995]. Patients at greatest risk for bladder cancer recurrence and/or tumor progression are those with low differentiated bladder carcinomas, multiple lesions in the bladder and the diagnosis of a carcinoma in situ or dysplasia of the bladder epithelium [Holmang, et al. 1995, Igawa, et al. 1996, Lacombe, et al. 1996]. Whether or not a second TUR after 2-6 weeks should be performed is still disputable; but, if the histological assessment from the first TUR remains unsure or the cell differentiation is low, then a second TUR or cystectomy is crucial to the prognosis [Rübben 2001]. An intravesical and percutaneous adjuvant therapy with bacillus Calmette-Guérin (BCG) has been reported by randomized studies of patients with controls to decrease bladder cancer recurrence, allow complete response rates of 70% and improve survival rates [De Jager, et al. 1991, Lamm DL 1992, Sarosdy and Lamm 1989]. Another randomized study comparing therapy with intravesical and subcutaneous BCG to intravesical doxorubicin also demonstrated improved response rates and less cancer recurrence [Lamm, et al. 1991]. Patients with widespread multifocal recurrent disease and/or other negative prognostic factors require other forms of treatment, such as radical cystectomy or interstitial implantation of radioisotopes [Catalona, et al. 1987, Coplen, et al. 1990, Herr 1991].

1.5.2 Invasive bladder carcinoma

Bladder carcinomas with TNM classifications of T2, T3 or T4 without lymph node or distant metastasis comprise approximately 20% of all initially diagnosed bladder cancers. The standard treatment for invasive tumors is the radical cystectomy, where the bladder, perivesical tissues, prostate gland and seminal vesicles in men are removed. The uterus, tubes, ovaries, anterior vaginal wall and urethra are removed in women [Olsson 1987]. Patients with a T2 classification can achieve about a 75% 5-year progressive free rate after a radical cystectomy. Among patients with deep infiltrative and less differentiated tumors is the 5-year progressive free rate of 20 to 40% [Smith JA 1988]. The presence of the tumor suppressor gene p53 shows an adverse

prognostic effect and predicts tumor recurrence among patients with T1, T2 or T3 tumors [Grossman, et al. 2003].

Due to high recurrence rate of 50% after radical cystectomy, the question on whether or not neoadjuvant chemotherapy prior to cystectomy is significant must be considered. According to a study by the Southwest Oncology Group which compared 3 cycles of neoadjuvant chemotherapy before cystectomy with cystectomy alone, T2 to T4a staged patients exhibited a borderline statistical significance in the 5-year survival rate [Grossman, et al. 2003]. The patients with the neoadjuvant chemotherapy prior to cystectomy showed a 5-year survival rate of 57% in comparison to the 43% among the group with cystectomy alone [Grossman, et al. 2003].

For those patients who cannot or are unwilling to undergo radical cystectomy, radiation treatment is an alternative. Although the patients experience side-effects such as dysuria, urinary frequency and acute toxic bowel effects during treatment, sexual dysfunction occurred less frequently, in comparison to the patients who underwent radical cystectomy [Henningsohn, et al. 2002]. Radiation therapy also permits a 5-year survival rate of 30% [Gospodarowicz, et al. 1989, Jahnson, et al. 1991, Yu, et al. 1985].

Chemoradiation therapy has been shown to improve the rate of local containment in locally invasive bladder carcinomas when compared to radiation therapy. However, chemoradiation does not improve overall survival or decrease the distant metastases rate [Coppin, et al. 1996]. Patients with T4a staging, lymph node metastases and/or distant metastases, progressive or recurrent invasive bladder cancer have a very poor prognosis. Treatment alternatives are radical cystectomy alone, irradiation, urinary diversion or adjuvant chemotherapy. Many studies have shown that methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) compared with other chemotherapy combinations, increased pathological response and median survival rates [Harker, et al. 1985, Logothetis, et al. 1990, Sternberg, et al. 1989].

1.6 Clinical reports

1.6.1 Symptoms

The leading symptom in 85-90% of patients diagnosed with bladder cancer is hematuria [Tanagho and McAninch 2000], which can be microscopic or gross. Unless otherwise proven, hematuria should be taken as a sign for tumors of the genitourinary tract. Other symptoms for bladder cancer include irritations of the bladder, such as dysuria, frequency and urgency. Since these symptoms are not specific to bladder cancer, a false diagnosis for cystitis or an upper vesical obstruction often occurs [München 2003]. Presence of bone or flank pain recurrently suggests metastases of the bone or retroperitoneum. Other signs of metastatic disease include hepatomegaly, supraclavicular lymphadenopathy and lymphedema [Tanagho and McAninch 2000].

1.6.2 Diagnostic procedures

1.6.2.1 Physical examination

The physical examination includes palpitation of the kidney, abdomen, rectum, prostate gland, ampulla of the rectum in men and a vaginal examination in women. Any lower abdominal tumors or pelvic infiltrations should be ruled out [München 2003].

1.6.2.2 Urinary and laboratory examinations

Hematuria is the most common pathological finding in the urine of patients with bladder cancer. A urine analysis can detect both gross and microscopic hematuria. Urine cultures are used to rule out urinary tract infections. In preparation for the transurethral resection of the bladder, coagulation values and blood counts should be determined. Studies have shown that the NMP22®Bladder Chek® test, which detects increased NMP22 protein levels in urine samples, in conjunction with cystoscopy, can enhance detection of bladder cancer [Grossman, et al. 2005, Ponsky, et al. 2001, Saad, et al.

2002]. Until further information has been collected, the NMP22®Bladder Chek® remains a non-routine test.

1.6.2.3 Abdominal sonography, intravenous urography, CT, MRI

Abdominal sonography may be used to rule out hydronephrosis, detect any upper urinary tract abnormalities and depending on size, can also detect up to 90% of bladder tumors [München 2003, Schuller, et al. 1982, Singer, et al. 1981]. Intravenous urography is most commonly used to assess the cause of hematuria and is mandatory in the pre-operative diagnostic. Hydronephrosis and bladder tumors, whether nonpapillary, infiltrating or papillary can also be recognized [Hatch and Barry 1986]. High staged tumors, that is T1 and above, require extra imaging such as CT and MRI to better determine the magnitude of bladder tumor infiltration, pelvic lymph node growth and differentiation from a bladder-confined or extravesical tumor [Tanagho and McAninch 2000].

1.6.2.4 Cystourethroscopy and transurethral resection

The diagnosis and clinical staging of bladder carcinomas is primarily done by cystourethroscopy and transurethral resection. Most superficial tumors are less than 3 cm in diameter, whereas higher-grade tumors are bigger. Erythematous regions and mucosal abnormalities may indicate a carcinoma in situ [Tanagho and McAninch 2000]. The ureteral artifices and prostatic urethra are also examined. When a tumor has been detected, a transurethral resection or biopsy is important in the tumor diagnosis. In the presence of a superficial tumor, the transurethral resection also serves as a curative treatment option.

1.6.2.5 Urinary cytology

Urine cytology examines exfoliated cells from both normal and neoplastic urothelial tissues in voided urine. If more cells are needed, an irrigation of an isotonic saline solution through a cystoscope or catheter can be done [Tanagho and McAninch 2000]. The advantage of this method lies in the possibility to obtain exfoliated cells from the interior of the entire bladder [München 2003]. The specificity of urine cytology for bladder cancer is high

but sensitivity is low; therefore, additional urine diagnostic tests should be followed [Bassi, et al. 2005].

1.6.2.6 Flow cytometry

The goal of flow cytometry is to detect increased DNA material in cell populations of exfoliated cells on glass slides after staining. About 80% of all bladder carcinomas can be identified through this procedure [Badalament, et al. 1988]. Together with urinary cytology, the two methods may be used to reveal bladder cancer recurrence and to control response rate in patients undergoing intravesical chemotherapy or irradiation [Badalament, et al. 1986, Klein, et al. 1982, Klein, et al. 1983].

1.6.2.7 Electoral procedures

Although cystoscopy and cytology remains the backbone for bladder cancer diagnosis, other methods are being tested and researched that are non-invasive. The non-invasive methods encompass analysis of certain molecular markers in voided urine. Tests include BTA Stat (Bard Diagnostic Sciences, Inc, Redmond, WA), BTA TRAK (Bard Diagnostic Sciences, Inc), NMP22 (Matritec Inc, Newton, MA), detection of telomerase action in exfoliated urothelial cells, evaluation of the Lewis X antigen on exfoliated urothelium and measurement of fibrinogen in urine (AuraTek FDP; PerImmune Inc, Rockville, MD).

1.7 Obesity and body mass index

Obesity has become a global health problem that many countries face. Due to unhealthy diets and lack of physical activity, the numbers of the overweight and obese have risen drastically in the last decade. The World Health Organization Europe has reported in year 2002 an increased risk of disease from a body mass index (BMI) of 20-22 kg/m^2, including diseases such as premature death, hypertension, coronary heart disease, hyperlipidaemia, stroke, diabetes mellitus type 2, cancer, osteoporosis, psychological and social problems. Although obesity is a worldwide challenge, the world health

report of 2002 has shown that Europe, at 26.5 kg/m^2, has the highest average BMI index of all WHO countries. According to the WHO, about 25-75% of the adult population in selected European countries are overweight. The prevalence in these countries is higher in women (around 30%) than in men (5-20%). The difference between the western and eastern European countries is almost non-existent. The most recent WHO Europe report reveals that approximately 400 million adults are overweight and around 130 million adults are obese.

The Body Mass Index is used to describe the weight and nutritional status among individuals [Garrow and Webster 1985]. According to the WHO, BMI is defined as the weight in kilograms divided by the height in squared meters.

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

The BMI indices below allows the derivation of the weight status and correlates with body fat; therefore, when reviewing the weight status, gender and age should be accounted for. Women tend to have more body fat than men with the same BMI, as older people may have a higher percentage of fat than younger generations [Gallagher, et al. 1996].

BMI (kg/m^2)	**Weight Status**
Below 18.5	Underweight
18.5 – 24.9	Normal
25.0 – 29.9	Overweight
30.0 and Above	Obese

1.8 Hypothesis

Obesity can have a fatal impact on health. The World Health Report of 2002 revealed the problems that can be caused by obesity, being respiratory difficulties, chronic osteoarthritis, skin problems and infertility. High BMI's are also linked to cardiovascular diseases, type 2 diabetes and certain cancer types, such as breast, colon, prostrate, endometrium, kidney and gallbladder cancer. Therefore, it is important to determine the role of BMI in cancer diagnosis, treatment and outcome. Does it make surgery more difficult? Should obese patients be advised against surgical treatment? What are the survival rates among patients undergoing surgery for cancer?

One could make the assumption that obese patients, in general, would have higher risk of complications before, during and after operations. Since the radical cystectomy involves reaching deep in the pelvic region, an increased mass of intraperitoneal fat not only aggravates the vision of the surgeon, but also complicates the intestinal mobilisation. Based on this belief, the question proposed is: does BMI affect bladder cancer patients undergoing radical cystectomy? By investigating the impact of BMI on symptoms before bladder tumor diagnosis, tumor progression, surgical conditions and complications, morbidity, mortality and survival, we hope to bring enlightenment.

2 Materials and Methods

Between the years 1986 and 2004 at the Technical University Clinic Rechts der Isar, 418 patients who underwent radical cystectomy after bladder cancer diagnosis were selected. 302 patients were men and 116 women. The ages ranged from 38 to 95 years old. These patients had BMI's between 14.03 and 38.34. 11 patients were underweight, 184 normal, 180 overweight and 43 obese, as defined by the WHO. A BMI less 18.5 is considered underweight, between 18.5 and 24.9 normal, between 25.0 and 29.9 overweight, and 30.0 and above obese. Bivariate and multivariate analyses were made between BMI and the various clinical parameters to determine any correlations.

A retrospective analysis of these patients marked the foundation of this dissertation. Data from each patient's file was typed into a folder in the Macintosh FileMaker Pro 4.1 software. For the documentation, the following points were selected: age, sex, height, weight, previous medical illnesses, medical history, date of transurethral resection of the bladder and/or radical cystectomy and any complications, pathological results after radical cystectomy and/or transurethral resection of the bladder, early (less than three months) and/or late (more than three months) complications after radical cystectomy, the choice of urinary diversion, follow-up questionnaires on quality of life after radical cystectomy, continence and satisfaction with the chosen urinary diversion. The follow-up questionnaires focused on the type of urinary diversion chosen, continence during the day and at night, and the patient's satisfaction. Due to the large amount of data concerning pre-operative symptoms, early and late complications after radical cystectomy, the most frequent parameters and its corresponding BMI were chosen and listed in a table drawn from Excel. The Excel table includes the minimum, 5-, 25-percentile, median, 75-, 95-percentile, maximum, mean, standard deviation and Mann-Whitney or Kruskal-Wallis test, depending on the number of comparative parameters. The tables were divided into six larger categories: pre-operative symptoms, tumor staging after TURB, tumor staging after radical cystectomy, early complications, late complications and continence after urinary diversion. The BMI was further categorized according to WHO

guidelines and compared to parameters, such as the number of transfused erythrocyte concentrates during radical cystectomy, duration of radical cystectomy and various urinary diversions, in bar graphs with error bars, which displayed mean and standard deviation. Numbers in bars indicated patient number in each group. Men and women were also compared to the whole study population. Local tumor relapse, tumor progression, metastasis, overall and disease specific survival was calculated with Kaplan-Meier from Sigma-Plot 2000 and Statistical Package for the Social Sciences 13.0 (SPSS). The mean, median, 5-year and 10-year survival rates for each BMI category was analyzed with the Kaplan-Meier formula. Standard deviation was also shown, unless otherwise indicated. The Log Rank (Mantel-Cox) test calculated a p-value to identify any significant or insignificant correlations between all four BMI categories and survival probability.

3 Results

3.1 Patient distribution

Among the 418 patients included in this retrospective analysis that were diagnosed with bladder cancer and treated with radical cystectomy, 302 were males and 116 were females. According to the WHO guidelines on weight status, 11 patients were underweight, 183 were normal, 181 were overweight and 43 were obese (figure 1). When looking at the whole patient collective, most of the patients were either normal (43.8%) or overweight (43.3%), meaning the BMI's ranged from 18.5 to 29.9 kg/m^2. Approximately 10.3% were obese and only 2.6% were underweight. Overall, the men were more inclined to being overweight than the women. The overall average age of the patients at time of radical cystectomy was 66.4 years, with the men being slightly younger than the women, respectively 65.5 and 69.0 years (figure 2). Between years 1986 and 2004, a steady increase of radical cystectomies in our clinic could be documented (figure 3). After closer observation of these patients, overweight patients (BMI 25.0-29.9 kg/m^2) are increasingly undergoing radical cystectomies.

3.2 Pre-operative symptoms

Tables 1-3 summarize the most common symptoms taken from the patients' medical histories before diagnosis of bladder cancer. A possible trend was seen between gross hematuria (p=0.24) and patients with higher BMI's, and dysuria (0.20) and patients with lower BMI's (table 1). Men, particularly those who experienced dysuria, presented with lower BMI's than their counterparts (p=0.10), although also without significance (table 2). The symptomatic women demonstrated a slight tendency to having increased BMI's (p=0.25), whereas; women who suffered from nocturia (p=0.05) exhibited an almost significant correlation to higher BMI's (table 3).

3.3 TURB - tumor staging and grading

Transurethral resection of the bladder is used to treat superficial bladder cancer and to obtain clinical staging of invasive bladder cancer. No significant correlation could be demonstrated between BMI category and tumor (p=0.74) or grading stages. Furthermore, no difference was seen when analyzing men and women separately (table 4). An interesting pattern, though statistically insignificant (p=0.52), could be seen from the bladder cancer grading data of the whole patient cohort, namely, as grading worsened, BMI increased from a mean of 23.78 kg/m^2 for G1-differentiated tumors to 25.53 kg/m^2 for G4-differentiated bladder cancer.

3.4 Radical cystectomy

3.4.1 Surgical duration

Due to the steady increase in radical cystectomies over the years, it is of increasing importance to analyze the duration of this surgical procedure. A decrease in duration of radical cystectomy between years 1986 and 2004 could be seen (figure 4), and the mean duration of radical cystectomy for each BMI group differs only slightly. Obese patients showed an insignificant increase over the other BMI groups in radical cystectomy time. Generally, the obese and overweight patients required more time for radical cystectomies (figures 5-6). The mean surgical time among 383 patients was 355±96 minutes (SD), ranging from 60 to 750 minutes. Upon examination of BMI category and length of radical cystectomy followed by reconstruction of ileal conduits and ileal neobladders, no significant correlation could be demonstrated (figure 7). Contrarily, when analyzing the four BMI categories within each urinary diversion (ileal conduit, ileal neobladder and others), obese patients showed prolonged surgical time, regardless of urinary diversion type (figure 8). Taken together, there was no significant association between BMI category, radical cystectomy duration and urinary diversion.

3.4.2 Blood transfusion rate

Blood loss, measured by amount of transfused erythrocyte concentrates, was also analyzed between years 1986 and 2004. Over the years and independent of BMI stage, a gradual decline in the number of transfused erythrocyte concentrates used could be observed (figure 9). A lesser decline of erythrocyte concentrate transfusion was seen among the BMI groups per year (figure 10). The number of erythrocyte concentrate bags (1 bag=250 ml) that were transfused during surgery ranged from 0 to 24. Among our patient cohort, those overweight (BMI 25.0-29.9 kg/m^2) required, on average, more blood transfusions during radical cystectomy than the others, followed from normal weight, obese and then underweight patients (figure 11). BMI category and type of urinary diversion also slightly affected the needed amount of transfused erythrocyte concentrates. In general, patients who received ileal conduits claimed more blood transfusions than those receiving ileal neobladders (figure 12). Among the patients who acquired ileal conduits, normal and overweight patients demanded more blood transfusions than obese and underweight patients. On the other hand, though without statistical significance, upon reconstruction of an ileal neobladder after radical cystectomy, obese patients needed more blood transfusions than underweight, overweight or normal weight patients. On average, women required fewer blood transfusions than men, regardless of urinary diversion method (data not shown). A significant association between rate of blood transfusion, type of urinary diversion, sex and BMI category could not be demonstrated.

3.4.3 Tumor staging and grading

After reviewing the outcomes from radical cystectomy, the TNM, grading and surgical margin parameters for bladder cancer exhibited insignificant associations to BMI category (table 5). On the contrary, our overweight patient collective significantly received more ileal neobladders than all other urinary diversions (p=0.00). Among the large selection of urinary diversions used after radical cystectomies, three categories were chosen for this retrospective analysis, namely ileal conduit, ileal neobladder and others (colon conduit,

hemi-kock pouch, Indiana pouch, ureterocutaneostomy and ureterosigmoidostomy). 165 of 403 patients received ileal neobladders and their mean BMI was 26.08 kg/m^2. This BMI was higher than those patients receiving ileal conduits and other urinary diversions. When analyzing the men and women separately, the men (table 6) demonstrated a trend between BMI category and urinary diversion (p=0.05). The heavier men (mean of 26.21 kg/m^2) received more ileal neobladders than their thinner counterparts. On the other hand, the women (table 7) exhibited a significant association between BMI category and confirmed distant metastasis (p=0.03). The heavier women (7 of 114), with a mean BMI of 26.55 kg/m^2, were staged with M1. Those women with no assessable or confirmed distant metastasis had an average BMI of 23.80 kg/m^2; therefore in our patient collective, at time of bladder cancer diagnosis, female patients with high BMI's were more likely to possess existing distant metastasis. The number of operated lymph nodes and tumorous lymph nodes did not correlate with the BMI category (no data shown).

3.5 Early complications after radical cystectomy

Complications occurring within 3 months after radical cystectomy are defined as "early" complications. All together, 260 from 283 patients reported the one or other form of complication (tables 8 and 9). The most common complications documented were wound healing disorders, ileus, gastro-intestinal symptoms, infections and cardiovascular complications. A significant relationship was seen between BMI group and hemorrhaging after radical cystectomy (p=0.02). The patients who suffered from this complication exhibited a mean BMI of 29.05 kg/m^2, compared to those without hemorrhages with a mean BMI of 25.18 kg/m^2. Generally, patients who suffered from a complication, except fistulas, anastomosis complications, neural impairment, infections and lymphoceles, exhibited higher BMI's than their non-symptomatic counterparts, although no significant correlations between BMI status and the complications could be seen. A likely trend exists between BMI category and incontinence (p=0.10). 16 of 283 patients who

suffered from incontinence had an average BMI of 26.83 kg/m^2, compared to those who did not report incontinence problems (mean BMI of 25.19 kg/m^2). Still, this trend did not prove to be significant.

The most common complications observed among the men were ileus, gastro-intestinal disorders, infections and cardiovascular complications (tables 10 and 11). When observing the male cohort, a significant association (p=0.03) appeared between BMI category and hemorrhage and hematoma. 7 of 209 male patients, with a mean BMI of 29.05 kg/m^2, hemorrhaged or endured hematomas, while those not suffering from these complications exhibited a mean BMI of 25.62 kg/m^2. The heavier male cohorts were at higher risk of hemorrhaging than the leaner cohorts after radical cystectomy. The 33 of 176 male patients, who suffered from ileus and/or gastro-intestinal disorders, presented a mean BMI of 26.39 kg/m^2. Patients not suffering from these complications were somewhat leaner (mean BMI of 25.62 kg/m^2). There might exist a slight trend, though insignificant, between developing an ileus and/or gastro-intestinal disorders and BMI (p=0.19). Male cohorts experiencing anastomosis complications and/or infections tended to be the "leaner" ones (mean BMI's of 24.38 kg/m^2 and 25.01 kg/m^2, respectively). Their heavier counterparts showed mean BMI's of 25.81 kg/m^2 and 25.83 kg/m^2, respectively. This trend between BMI and anastomosis complications and infections remained insignificant (p=0.22 and p=0.23, respectively).

Ileus and/or gastro-intestinal disorders were most commonly detected among the female cohorts (tables 12 and 13). The women demonstrated an almost significant correlation between BMI and wound healing disorders (p=0.05). The female patients (6 of 74) who experienced wound-healing disorders, such as fascia dehiscence, had higher BMI's (mean of 27.37 kg/m^2) than patients without wound healing problems (mean BMI of 23.68 kg/m^2).

3.6 Late complications after radical cystectomy

Complications occurring 3 months or later following radical cystectomy are defined as "late" complications. Analysis of the whole patient collective (table 14) showed no significant association between BMI and late complications.

An insignificant trend could be seen between BMI and three late complications, namely stones, urinary tract infection and cerebral apoplexy (p=0.08, p=0.10 and p=0.15, respectively). Patients who reported having stones (17 of 39) and urinary tract infections (79 of 169) were those with higher BMI's (mean BMI 26.87 kg/m^2 and 25.49 kg/m^2, respectively). Patients with no stones had an average BMI of 24.94 kg/m^2. Cohorts who did not suffer from urinary tract infections had an average BMI of 24.75 kg/m^2. Surprisingly though, 2 of 52 patients who experienced cerebral apoplexy had a mean BMI of 20.98 kg/m^2, meaning the thinner patients were more inclined to acquiring cerebral apoplexy than the heavier patients (mean BMI of 25.42 kg/m^2).

The male cohorts (table 15) showed insignificant trends between BMI status and three late complications, namely stones (p=0.07), fistulas (p=0.08) and infections (p=0.17). The infections include fever, abscess, leukocytosis, pancreatitis, pyelonephritis, pneumonia and sepsis. 13 of 107 men with stones presented an average BMI of 27.23 kg/m^2, compared to 25.21 kg/m^2. The same trend was seen with the 2 of 55 men experiencing fistulas. The two men had a mean BMI of 30.31 kg/m^2, while those without fistulas had mean BMI of 26.10 kg/m^2. Interestingly, the opposite trend was demonstrated between BMI category and infections, but was also insignificant. The men that did not suffer from infections were those that exhibited a higher average BMI (26.23 kg/m^2 compared to 25.06 kg/m^2).

The female cohorts (table 16) demonstrated a significant correlation between BMI stage and acidosis (p=0.00). The women (11 of 38) encountering acidosis were heavier than their counterparts (28.18 kg/m^2 and 23.02 kg/m^2, respectively). In other words, women in our patient collective who presented higher BMI's were more likely to develop acidosis after radical cystectomy. A trend was also seen between BMI category and urinary tract infections (p=0.07). Overweight women (mean BMI of 25.03 kg/m^2) were more inclined to suffer from urinary tract infections, although without significance.

3.7 Continence and satisfaction

Follow-up questionnaires were designed to collect data from patients on daytime and nocturnal continence, quality of life and satisfaction of the chosen urinary diversion. No significant association between BMI category and these parameters were found (table 17).

3.8 Survival probability

3.8.1 Overall survival rates

The mean survival time for the whole cohort was 99.0±5.5 months. The underweight patients (n=9) demonstrated the least mean survival time of 66.3±17.5 months; whereas, the overweight patients (n=162) had the longest mean survival time of 105.7±7.5 months followed by the obese patients (n=38) with 92.6±15.3 months and the normal weight patients (n=159) with 86.6±8.1 months. The estimated 5-year survival rates for underweight, normal weight, overweight and obese patients were 62.2%±17.8%, 46.6%±4.2%, 57.3%±4.5% and 49.9%±8.5%, respectively, and the 10-year survival rates were not available, 37.0%±4.7%, 43.7%±5.4% and 36.0%±10.8%, respectively (figure 13). A p-value of 0.076 showed a slight trend with no significance between BMI category and survival probability; but, upon exclusion of the underweight population, a significant relationship between BMI and survival time could be seen (p=0.032). In our patient collective, overweight patients had significantly better chances for longer survival than obese and normal weight patients.

The male cohorts (n=270) presented an overall mean survival time of 104.0±6.5 months (figure 14). Obese men (n=32) survived, on the average, longer than the others (mean 103.1±16.7 months). Mean survival times of normal (n=107) and overweight (n=127) men could hardly be differentiated (mean 95.0±9.8 months and 95.9±7.2 months, respectively). Underweight men (n=4) died after an average survival time of 53.5±20.9 months, when

undergoing radical cystectomy. The 5-year survival rate among the normal weight, obese and overweight male patients were 52.6%±5.1%, 55.7%±5.2% and 57.0%±9.1%, respectively. The estimated 10-year survival rate among the underweight, normal weight, obese and overweight patients were not available, 39.3%±5.8%, 45.7%±5.7% and 41.1%±12.1%, respectively. With a p-value of 0.426, no significant association between BMI status and survival rate could be demonstrated. After comparing only the normal and overweight male patients after radical cystectomy, a p-value of 0.453 also showed an insignificant association between BMI group and survival probability.

On the other hand, the whole female collective (n=98) showed a slight trend between BMI stage and survival probability (p=0.084). Their overall mean survival time was 81.1±9.3 months. The overweight females (n=35) survived the longest, with a mean survival time of 110.0±15.0 months, while the obese females (n=6) died after a mean survival time of 21.2±7.5 months (figure 15). The 5-year survival rate of overweight women (62.8%±8.8%) was clearly higher than the normal weight (33.6%±7.3%) and obese females (33.3%±19.2%). With a standard deviation of 24.8%, underweight women (n=5) presented a 5-year survival rate of 53.3%. However, since the underweight and obese women populations consisted of very small numbers, no statistical calculations could be made. When comparing only the normal and overweight female populations, a significant advantage of overweight females could be detected (p=0.037).

Upon comparison of survival probability between males (n=270) and females (n=98), a trend (p=0.065) was found between the two sexes and radical cystectomy. Overall, the men lived longer than the women (figure 16), with mean survival times of 104.0±6.5 months and 81.1±9.3 months, respectively. The 5-year survival rate was evidently the lowest for the women (43.4%±5.5%) and highest for the men (55.1%±3.4%), as was the 10-year survival rate (35.1%±6.3% and 41.8%±4.0%, respectively).

3.8.2 Tumor-related survival rates

A significant correlation (p=0.752) between BMI category and death caused by bladder cancer was not found among the patient collective (figure 17). 61 of 279 patients died from bladder cancer between the years 1986 and 2004. The obese patients (n=28) survived, on average (mean survival time of 153.9±15.0 months) longer, followed by normal weight (n=111), overweight (n=134) and lastly, underweight patients (mean survival of 151.1±9.3 months, 149.3±7.1 months and 96.5±17.2 months, respectively). The number of underweight patients must also be noted (n=6). The overall mean survival time for all BMI groups was 157.2±5.7 months.

From a total of 240 patients that were documented, 14 patients developed local tumor recurrence. Due to the small cohort population, no median or mean values could be calculated. 98 were normal weight, 113 overweight and 24 obese. None of the 5 underweight patients relapsed. With a p-value of 0.306, BMI status did not significantly correlate to survival among patients who relapsed. The overall survival rate was highest among the underweight patients (100%). The obese had the lowest survival rate of about 83.3%±15.2% and overweight patients were better off than normal weight patients (survival probability of 95.0%±2.6% and 89.6%±3.6%, respectively). These observations remained insignificant (figure 18), as was the relationship between normal and overweight patients developing local tumor relapses and BMI (p=0.409).

Tumor progression occurred in 72 from 248 reported patients. 101 normal weight, 117 overweight, 25 obese and 5 underweight patients experienced tumor progression. The overweight cohort presented the highest mean survival time of 141.9±7.8 months, whereas, the underweight population exhibited the lowest mean survival time of 92.5±20.4 months. The overall mean survival time among all BMI groups was 143.5±6.3 months. No significant relationship (p=0.334) existed between BMI level and survival probability, among tumor-progressive patients (figure 19). When examining only the normal and overweight patients with tumor progression, an insignificant trend was demonstrated (p=0.075).

Of the 248 patients reporting metastasis, 101 were normal weight, 117 overweight, 25 obese and 5 underweight. The mean survival time ranged from 92.5±20.4 to 149.2±16.5 months (underweight and obese, respectively). Upon observation of the survival probability between the four BMI categories, an insignificant association was seen among those cohorts who developed metastasis (p=0.853). The survival probability is shown in figure 20.

3.8.3 Urinary diversion survival rates

Three groups were formed for the type of urinary diversion chosen after radical cystectomy, namely ileal conduit, ileal neobladder and others. Survival probability (p=0.000) significantly correlated to the type of urinary diversion chosen (figure 21). Patients, who received ileal neobladders after radical cystectomy had the highest mean survival time of 132.8±8.3 months, followed those receiving other urinary diversions and ileal conduits (mean survival time of 102.6±13.0 months and 67.6±7.0 months, respectively). Furthermore, patients with ileal neobladders presented a 5-year survival rate of 69.1%±4.7%, compared to those with other urinary diversions (55.2%±7.7%) and ileal conduits (36.3%±4.0%). The 10-year survival rates were also calculated for patients receiving ileal neobladders, other urinary diversions and ileal conduits (60.2%±5.5%, 44.7%±7.8% and 25.3%±4.2%, respectively). A total of 169 patients received ileal conduits. Obese (n=21) and overweight (n=64) patients presented mean survival times of 76.7±18.4 and 75.6±10.9 months; whereas, normal weight (n=80) and underweight (n=4) patients demonstrated mean survival times of 56.8±8.7 and 58.7±28.3 months (figure 22). Although results show that obese patients with ileal conduits have prolonged survival rates, this association remains insignificant (p=0.480). Among patients receiving ileal conduits, a comparison between obese and overweight patients (p=0.864), normal and overweight patients (p=0.136) and lastly, normal and obese patients (p=0.387) all demonstrated insignificant associations between BMI category and survival rates.

The same pattern was seen in ileal neobladder recipients, with the exception of normal and overweight patients. The p-value between these two cohorts was 0.086, which leads to a conclusion that overweight patients may have an

insignificant advantage to their normal weight ileal neobladder recipient counterparts. The analyses between obese and overweight (p=0.894) ileal neobladder recipients and between normal and obese (p=0.394) patients showed insignificant associations between BMI and survival probability among ileal neobladder recipients. In general, no significant relationship (p=0.318) could be seen between all BMI groups and survival probability among patients receiving ileal neobladders (figure 23).

Due to the small number of patients receiving other urinary diversions (n=43), a statement on the significance between BMI and survival rate could not be made (figure 24).

4 Discussion

Obesity has become a worldwide epidemic during the past two decades. This dilemma applies both to adults and adolescents. In the years 2003 and 2004, approximately 17.1% of American children were overweight, 32.2% adults were obese and 5% adults were extremely obese. While the prevalence of obesity in women remained unchanged between 1999 and 2004 (33.4% to 33.2%, respectively), obesity among men increased significantly from 27.5% to 31.1% [Ogden, et al. 2006]. Not only does obesity rank number seven in leading causes of death in the United States, obesity has a negative impact socially, economically and on health, such as developing diabetes mellitus, cardiovascular diseases, hypertension and cancer [Wellman and Friedberg 2002]. Since studies have shown that subjects with BMI's from 22.0 to 24.9 kg/m^2 are also at risk of developing chronic diseases, it may be wise to suggest that adults maintain a BMI between 18.5 and 21.9 kg/m^2 to reduce this risk [Field, et al. 2001]. In the year 2000, the yearly health care costs resulting from overweight and obesity was estimated at $117 billion [Mokdad, et al. 2004]. High BMI's also influence costs at work, showing that overweight and obese employees were more likely to call in sick or claim disability [Schmier, et al. 2006]. Wellman and Friedberg estimated yearly obesity-related costs lost at 40 million productive workdays, 63 million visits to the doctor, 239 million activity-restricted days and 90 million bedridden days.

Results from the 1989 WHO's MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) project reported a higher prevalence of obesity among women, whereas men were more overweight [Varo, et al. 2002]. According to WHO Europe 2002, the gap in prevalence of obesity is closing rapidly between Western and Eastern Europe; furthermore, an increase of 20 million obese people is estimated for the next five years. Notably, one in thirteen deaths in the European Union is more than likely overweight- and/or obesity-related [Banegas, et al. 2003].

Due to these alarming statistics, it is clear that obesity is playing an ever more important role in the lives of all people. With the increase of deaths caused by cancer every year, the association between BMI and cancer is also

substantial. According to data from years 2002 and 2003 collected by the American Institute for Cancer Research (AICR), obesity increases by about 25% to 33%, the risk of developing breast, colon, endometrial, esophageal, kidney or prostate cancer [Amling, et al. 2001, Bjorge, et al. 2004, Engeland, et al. 2005, Wenten, et al. 2002, Xu, et al. 2002]. In a Swedish study, obese subjects showed a 33% increase in cancer incidence, with 37% in women and 25% in men [Wolk, et al. 2001]. The Canadians showed that high BMI's resulted in 7.7% of all cancers, with 5.9% in women and 9.7% in men [Pan, et al. 2004]. Findings from these and other studies demonstrated a significant association between high BMI's and risk of carcinomas of the kidney, colon, pancreas, ovary, rectum, small intestine, cervix, breast and prostate [Pan, et al. 2004, Patel, et al. 2005, Pischon, et al. 2005, Wolk, et al. 2001].

Although obesity does not seem to be a risk factor for developing bladder cancer, it is still critical to analyze the role of BMI in patients who underwent radical cystectomies after bladder cancer diagnosis. Bladder cancer is the fourth most commonly diagnosed cancer among men and the ninth in women [Lerner 2005]. The American Cancer Society estimated that 61,420 people will be diagnosed with bladder cancer and 13,060 will die from bladder cancer in 2006. By 2010, the prevalence of bladder cancer will have increased by about 28% in the USA (Wendy Sheridan from Bladder Cancer Webcafe 2006). From the years 2000 to 2003, SEER (Surveillance Epidemiology and End Results) calculated that 4.3 out of 100,000 people in America died from urinary bladder cancer.

4.1 BMI and pre-operative symptoms

Little has been published on correlations between BMI and severance and duration of symptoms of patients, especially during the time prior to physician consultation or visit. Since overweight and obese people are often more ashamed of their bodies, one could expect they would wait until the symptoms were severe before seeking medical advice, as shown among obese women who were less likely to attend cancer screenings for colorectal, breast and cervical cancers [Rosen and Schneider 2004, Wee, et al. 2004, Wee, et al.

2005]. A possible explanation could lie in the observation that overweight and obese persons are more inclined to be ashamed of their bodies [Wellman and Friedberg 2002].

Our patient collective showed no significant association between high BMI's and pre-operative symptoms, such as gross hematuria and dysuria. An almost significant relationship existed between nocturia and high BMI's among women of our patient collective, which could be supported by the findings from a study of Finnish patients, where an association between obesity and increased nocturia was found especially among the women population [Tikkinen, et al. 2006]. This observation might therefore be non-tumor-related.

4.2 BMI and tumor staging

One could speculate that, due to delayed physician consultation from obese patients because of shame and maybe even ignorance, this population would have worse TNM-staging, in comparison to non-obese patients.

After examining our patient cohort, no distinct association was found between BMI and TNM classification, neither after TURB nor radical cystectomy. Accordingly, it has been demonstrated among renal cell carcinoma patients, that obese patients, in comparison with normal weight patients and at time of diagnosis, were not at higher risk of developing advanced renal cell cancer [Schips, et al. 2003].

It has been shown that overweight and obese patients have high amounts of vascular growth factors, which may all contribute to risk of metastatic disease among obese patients with cancer [Silha, et al. 2005]. Among our patient cohort, women who presented with distant metastasis (M1) were heavier than those with M0/Mx. However, this correlation could not be seen in the male patient cohort. Similarly, no correlations could be demonstrated between BMI and advanced prostate cancer [Schuurman, et al. 2000].

Certain technical adverse circumstances, such as exposure and coagulation difficulties, have been noted in overweight and obese patients [Raiga, et al. 2000], which leads to the assumption that these patients would have a lower probability of receiving a "clean-cut" radical cystectomy leaving tumor-free

resection margins. Operative difficulties among obese prostate cancer patients have resulted in higher risk of postitive surgical margins, which in turn lead to higher mortality [Freedland, et al. 2006]. Our findings were unable to confirm this observation, since our overweight and obese patients did not exhibit more positive resection margins than normal or underweight patients.

It has been shown that with increasing BMI, the risk of high-grade prostate and breast cancer also increases [Cui, et al. 2005, Freedland, et al. 2005a, Freedland, et al. 2005b, Rohrmann, et al. 2003]. Patients with BMI 35 kg/m^2 or more were more likely to develop high grade tumors, leading to less survival following radical prostatectomy [Freedland, et al. 2004]. We were unable to demonstrate a significant correlation between BMI and grading of bladder carcinomas.

However, since increasing BMI and age are obstacles that may aggravate staging procedures, surgeons need to recognize the role of BMI as a potential risk factor in all cancers when performing staging [Cox, et al. 2002, Derossis, et al. 2003].

4.3 BMI and intraoperative difficulties

Lee et al. showed that increased BMI was independently related to increased blood loss, prolonged surgical duration and higher risk for complications among bladder cancer patients receiving radical cystectomies [Lee, et al. 2004]. Obesity likewise increased, significantly, surgical duration and blood loss in patients undergoing distal gastrectomy for gastric cancer [Kodera, et al. 2004]. Among renal cell carcinomas patients undergoing radical nephrectomy, blood loss and operative time also increased significantly with increasing BMI [Donat, et al. 2006]. A similar significant observation between obese patients, undergoing vaginal or abdominal hysterectomy, and prolonged surgical time and increased peri-operative blood loss was seen [Rasmussen, et al. 2004]. Furthermore, an excess of intraperitoneal adipose tissue contributed to surgical difficulties, such as exposure and coagulation complications [Raiga, et al. 2000]. The overweight and obese subjects from our patient collective, however, showed only insignificantly, prolonged

operative times and required on the average, more blood transfusions during radical cystectomy. This observation slightly contradicts the feared assumption that high BMI's lead to extensively increased operative risk, as is seen among patients who underwent gastrectomy for gastric cancer [Barry, et al. 2003]. In another study, BMI was shown to be the only pre-operative parameter from those analyzed (BMI, co-morbid illnesses and patient demographics) that could predict blood loss during radical cystectomy and that the overweight and obese patients did not necessarily exhibit increased complication risks or longer stay in the hospital [Chang, et al. 2004].
However, one must not forget that overweight, obese and the morbidly obese patients are subjected to increased somatic and psychiatric co-morbidities, that could further impair peri-operative recovery [Buddeberg-Fischer, et al. 2006].

4.4 BMI and complications

Complications occurring after radical cystectomy for bladder cancer may be categorized as being early or late (< 3 months or ≥ 3 months after radical cystectomy, respectively).
From the compiled list of early complications occurring after radical cystectomy, hemorrhaging was significantly associated with BMI, when observing the whole patient collective. Interestingly, a near significant association was seen only among our women patient cohort between BMI and wound healing disorders, such as fascia dehiscence. Studies have shown that morbid obesity increases intra-abdominal pressure [Lambert, et al. 2005], which may lead to abdominal wound healing difficulties [Diebel, et al. 1992]. Since little data concerning post-operative complications after radical cystectomy was found, findings from other fields, such as gynecological, transplantation and abdominal surgery were used to help demonstrate any possible correlations between BMI and post-operative complications. To begin with, no significant relationship between BMI and hemorrhaging, infection or increased hospital stay could be demonstrated among obese patients undergoing vaginal or abdominal hysterectomy [Rasmussen, et al. 2004].

Contrarily, patients with BMI's greater than 35 kg/m^2, undergoing primary cesarean delivery, showed a higher incidence of wound complications [Wall, et al. 2003]. Complications such as, post-operative bleeding, wound infection and fascia dehiscence have also been found to be significantly related to patients with BMI's ≥ 30 kg/m^2, following pancreas transplantation [Hanish, et al. 2005]. BMI also played an important role in post-operative complications after abdominal surgeries, such as gastric bypasses, pancreatectomies, colectomies and gastrectomies. The morbidly obese suffered from more post-operative complications after Roux-en-Y bypass than their peers [Gonzalez, et al. 2003]. Moreover, patients with BMI's > 25 kg/m^2 developed significantly more intra-abdominal infections after distal pancreatectomies for pancreas cancer than the thinner patients [Sledzianowski, et al. 2005]. Intra-abdominal post-operative infections were also significantly increased in obese patients undergoing left colectomies for colon cancer [Benoist, et al. 2000]. Similarly, patients with BMI ≥ 27 kg/m^2 after distal gastrectomy for gastric cancer, showed elevated intra-abdominal infections, which lead to significantly longer hospital stays [Kodera, et al. 2004].

Upon observation of the late complications after radical cystectomy, only our women cohort exhibited a significant correlation between BMI and developing acidosis and an insignificant trend between BMI and urinary tract infections. It has been shown that employment of ileum or colon in urinary tract reconstruction most often leads to metabolic acidosis, due to deviations of the normal physiological function of the mucous membrane in that region. The ileum and colon absorb ammonium and chloride ions and lose potassium ions through the mucous membrane [Tanrikut and McDougal 2004]. In the Na^+/H^+ antiport system, ammonium displaces sodium and chloride ions are reabsorbed when bicarbonate ions are excreted, leading to a total gain of chloride ions, but a total loss for bicarbonate ions, resulting in a metabolic imbalance [McDougal, et al. 1995, Stampfer and McDougal 1997]. Due to a higher volume of residual urine in an ileal neobladder, complications for infection, stone deposits and acidosis were therefore increased [Khafagy, et al. 2006]. Why only women in our study suffered more from acidosis remains unknown.

4.5 Survival

4.5.1 Overall survival

Overweight patients in our study showed significantly longer survival rates after radical cystectomy than obese and normal weight patients. Also, we observed in overweight women significantly prolonged survival rates compared to normal weight female patients, whereas this correlation remained insignificant in the male population. Chang et al. and Hafron et al. showed no significant association between BMI and overall or disease specific survival in bladder cancer patients after undergoing radical cystectomy, but Hafron et al. was able to demonstrate a possible trend in normal weight patients (BMI < 25 kg/m^2) to better bladder cancer survival [Chang, et al. 2004, Hafron, et al. 2005]. To this time, little data concerning BMI and survival, after radical cystectomy, has been gathered.

Relationships between BMI and survival in other cancers have been studied, which have also demonstrated obesity as being advantageous in cancer survival. For example, the survival of patients with renal cell cancer was in favor of the overweight and obese population after nephrectomy [Kamat, et al. 2004, Schips, et al. 2004]. The same effect was further observed among obese patients diagnosed with ovarian cancer [Purdie, et al. 2001], female overweight patients with esophageal adenocarcinoma, non-cardia gastric adenocarcinomas [Trivers, et al. 2005] and middle-aged men with prostate cancer [Porter and Stanford 2005]. Moreover, further studies have also shown that obesity was not a criterion for adverse prognosis of breast [Carmichael, et al. 2004], lung, prostate and colon cancer [Eichholzer, et al. 2005].

Interestingly, being too thin is likewise just as unhealthy as being too fat. Thin patients have been shown with higher breast cancer mortality rates than the obese [Maehle, et al. 2004]. Furthermore, the Fred Hutchinson Cancer Research Center in Seattle, Washington, USA released a report on March 14, 2006 stating that underweight and obese postmenopausal women diagnosed with colorectal cancer had higher mortality rates than the other women. Additionally, among women with certain stages of colon cancer and non-

smoking women with breast cancer, a significant association between elevated BMI's and higher overall mortality rates was demonstrated [Kroenke, et al. 2005, Meyerhardt, et al. 2003].
Therefore, while the emphasis today is on the effects of obesity, both extreme poles (underweight and obesity) of BMI are likely to have negative impact on the outcome after radical cystectomy.

4.5.2 Tumor-related survival

From the patients in our study, no significant correlation was found between BMI and death from bladder cancer, as were the associations between BMI and local tumor recurrence, tumor progression and metastasis.
BMI plays an important role in tumor growth and proliferation [Otani, et al. 2005], suggesting that high BMI's could lead to a higher risk of tumor relapses, progression and metastasis. One study showed that male rectal cancer patients with elevated BMI's have higher risks of local tumor recurrence [Meyerhardt, et al. 2004]. A nearly significant increase in tumor relapse was also seen among obese women with certain stages of colon cancer [Meyerhardt, et al. 2003]. Furthermore, in women with breast cancer, especially the non-smokers, an increase in BMI lead to more tumor recurrences [Kroenke, et al. 2005]. A significant correlation was also demonstrated between increasing BMI and tumor recurrence in patients after radical prostatectomy for prostate cancer [Bassett, et al. 2005].
Lastly, obesity not only correlates with high grade prostate cancer, but also with increased tumor recurrences after radical prostatectomy [Amling, et al. 2004]. On the contrary, new findings have shown that thinness could also be linked to local recurrence of breast cancer [Marret, et al. 2001] and that high BMI's did not necessarily have a negative impact on tumor progression among renal cell carcinoma patients undergoing nephrectomy [Donat, et al. 2006].

4.5.3 Urinary diversion-related survival

Our results showed no significant association of survival probability between BMI and type of urinary diversion (ileal conduits, ileal neobladders and

others). Although our findings indicated longer survival rates of obese patients with ileal conduits, this correlation remained insignificant. While one study showed that the obese received more incontinent urinary diversions [Lee, et al. 2004], our data showed that high BMI patients received more ileal neobladders followed by ileal conduits and other urinary diversions. Chang et al. found no correlation between BMI and type of urinary diversion, suggesting that survival probability of obese patients with a certain type of urinary diversion might also not be affected by BMI [Chang, et al. 2004].

Many factors may contribute to the survival rate of a patient after radical cystectomy followed by urinary reconstruction. For example, biological age of patient, body physique and status, mental status, kidney functions, pathological stage of bladder cancer, intestinal pathology, history of radiation, chemotherapy, surgeon expertise and experience and last but not least, patient fears and preference should be taken into consideration when deciding the type of urinary diversion needed [Ahlering, et al. 1989]. Although there is no consensus for choosing the best or “right” type of urinary diversion [Benson and Olsson 1992], the orthotopic neobladder is recommended the most [Burkhard, et al. 2006].

Recapitulating, more studies need to be done to determine whether BMI affects survival probability of bladder cancer patients in conjunction with urinary diversions.

4.6 Concluding remarks

In summary, obesity plays an ever-increasing role in medicine. Due to the growing population of overweight and obese people and the adverse effects of being fat, it is even more important to analyze the exact role obesity has on risk of cancer and cancer survival. We must not forget that obesity can be inhibited, which means that prevention of obesity is just as important as finding correlations between BMI and cancer mortality. However, to improve peri- and post-operative management of overweight and obese patients, as well as quality of life and cancer survival, further studies should be undertaken.

5 Summary

The rising worldwide epidemic of obesity not only causes health problems like cardiovascular diseases, type 2 diabetes or is a risk factor for certain malignant tumors (e.g. breast, colon, endometrium or kidney cancer), but also may influence postoperative outcomes after tumor surgery. As bladder cancer is the ninth most frequent malignant tumor worldwide, it is also of interest to analyze the impact of patients´ body mass index (BMI) on the outcome after radical sugery because of bladder cancer.

In our study, the overweight and obese patients did not exhibit more pre-operative symptoms, higher tumor staging after transuretheral resection and after radical cystectomy or an increased rate of complications. Surgical time and volume of blood transfusions (among ileal neobladder recipients) were increased with higher BMI, but again without significance. Upon exclusion of underweight patients, a significant increase of survival for overweight patients after radical cystectomy could be demonstrated. Furthermore, survival probability significantly correlated to the type of urinary diversion chosen. No significant associations, among our patients, were seen between BMI and tumor specific survival, rate of local tumor recurrence, tumor progression or metastasis.

Even though many studies have shown that obesity considerably increases risk of cancer development and decreases the survival probability of cancer patients, in our study high BMI did not significantly affect survival outcomes of patients who underwent radical cystectomy for bladder cancer. Therefore, elevated body mass indices should not per se be a prominent factor in deciding against radical cystectomy for bladder cancer.

6 Tables

Table 1a: Pre-operative symptoms 1: Mann-Whitney test 2: Kruskal-Wallis test

All patients	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Symptoms	**yes**	391	14.03	19.79	23.12	**25.22**	27.55	31.53	38.34	**25.41**	3.65	**0.51** [1]
	no	21	19.26	19.40	21.63	**25.10**	27.10	28.41	30.10	**24.61**	3.25	
Gross hematuria	**yes**	305	14.03	20.07	23.18	**25.40**	27.48	31.31	38.34	**25.48**	3.59	**0.24** [1]
	no	107	18.02	19.21	22.62	**24.93**	27.55	31.78	37.04	**25.04**	3.73	
Dysuria	**yes**	112	16.71	19.90	23.00	**24.97**	26.89	31.60	34.69	**25.01**	3.41	**0.20** [1]
	no	300	14.03	19.53	23.12	**25.40**	27.70	31.33	38.34	**25.50**	3.70	
Nocturia	**yes**	188	16.07	20.30	23.49	**25.39**	27.45	31.80	37.04	**25.55**	3.44	**0.40** [1]
	no	224	14.03	19.28	22.84	**25.01**	27.57	31.12	38.34	**25.21**	3.78	
Pain	**yes**	46	16.71	18.53	22.93	**25.07**	27.11	29.66	32.95	**24.81**	3.44	**0.46** [1]
	no	366	14.03	19.62	23.11	**25.22**	27.57	31.53	38.34	**25.44**	3.65	
Obstructive urinary symptoms	**yes**	46	19.03	20.35	23.20	**25.38**	26.95	31.74	37.04	**25.65**	3.61	**0.76** [1]
	no	366	14.03	19.55	23.04	**25.18**	27.55	31.33	38.34	**25.33**	3.63	
Urinary tract infection	**yes**	30	16.71	19.06	22.48	**24.11**	27.67	30.91	31.90	**24.72**	3.81	**0.34** [1]
	no	382	14.03	19.71	23.14	**25.29**	27.53	31.52	38.34	**25.42**	3.61	
Incontinence	**yes**	29	19.03	20.59	23.12	**24.44**	27.69	30.35	32.87	**25.16**	3.33	**0.60** [1]
	no	383	14.03	19.54	23.08	**25.25**	27.51	31.51	38.34	**25.38**	3.65	

Table 1b: Pre-operative symptoms

Men	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Symptoms	**yes**	282	14.03	21.01	23.64	**25.56**	28.04	31.90	38.34	**25.94**	3.49	**0.94** [1]
	no	15	20.83	21.37	23.53	**26.33**	27.61	28.92	30.10	**25.56**	2.84	
Gross hematuria	**yes**	232	14.03	21.15	23.88	**25.63**	28.03	31.89	38.34	**26.02**	3.47	**0.36** [1]
	no	65	18.02	20.58	23.44	**25.18**	27.76	31.25	37.04	**25.54**	3.42	
Dysuria	**yes**	75	17.30	20.78	23.21	**25.00**	27.35	31.96	34.69	**25.39**	3.35	**0.10** [1]
	no	222	14.03	21.06	24.01	**25.76**	28.08	31.53	38.34	**26.10**	3.49	
Nocturia	**yes**	134	17.30	21.53	23.78	**25.56**	27.55	32.00	37.04	**25.89**	3.33	**0.85** [1]
	no	163	14.03	20.78	23.54	**25.61**	28.08	31.51	38.34	**25.94**	3.58	
Pain	**yes**	29	17.30	20.94	24.11	**25.99**	27.46	30.44	32.95	**25.87**	3.23	**0.70** [1]
	no	268	14.03	21.02	23.52	**25.55**	28.01	31.90	38.34	**25.92**	3.49	
Obstructive urinary symptoms	**yes**	38	20.06	21.93	23.29	**25.56**	27.38	32.04	37.04	**26.07**	3.61	**0.97** [1]
	no	259	14.03	20.86	23.77	**25.56**	28.02	31.57	38.34	**25.89**	3.44	
Urinary tract infection	**yes**	14	21.39	22.36	23.29	**27.16**	28.81	31.54	31.90	**26.66**	3.40	**0.39** [1]
	no	283	14.03	20.88	23.65	**25.54**	27.77	31.89	38.34	**25.88**	3.46	
Incontinence	**yes**	16	22.41	22.75	23.37	**25.02**	28.15	31.45	32.87	**26.10**	3.24	**0.99** [1]
	no	281	14.03	20.87	23.67	**25.61**	28.01	31.89	38.34	**25.91**	3.48	

Table 1c: Pre-operative symptoms

Women	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Symptoms	**yes**	109	16.07	18.17	21.40	**23.78**	26.35	30.10	34.84	**24.03**	3.69	**0.25** [1]
	no	6	19.26	19.29	19.43	**21.84**	24.77	25.84	26.13	**22.24**	3.18	
Gross hematuria	**yes**	73	16.07	18.02	21.40	**23.78**	26.22	29.25	30.82	**23.76**	3.45	**0.79** [1]
	no	42	18.03	19.03	21.12	**23.79**	27.19	31.77	34.84	**24.26**	4.07	
Dysuria	**yes**	37	16.71	18.96	21.48	**24.80**	26.18	29.58	32.27	**24.24**	3.44	**0.48** [1]
	no	78	16.07	18.28	21.09	**23.56**	26.29	29.71	34.84	**23.80**	3.80	
Nocturia	**yes**	54	16.07	19.08	22.26	**24.81**	26.34	29.98	34.84	**24.66**	3.57	**0.05** [1]
	no	61	16.53	18.03	20.31	**23.14**	26.13	29.41	31.89	**23.30**	3.68	
Pain	**yes**	17	16.71	17.80	21.09	**23.24**	25.39	27.23	27.74	**23.01**	3.08	**0.33** [1]
	no	98	16.07	18.92	21.27	**24.01**	26.54	30.48	34.84	**24.10**	3.76	
Obstructive urinary symptoms	**yes**	8	19.03	19.09	21.92	**24.81**	26.12	26.19	26.22	**23.64**	3.01	**0.91** [1]
	no	107	16.07	18.14	21.16	**23.74**	26.48	30.19	34.84	**23.96**	3.73	
Urinary tract infection	**yes**	16	16.71	18.45	20.79	**23.62**	24.73	28.21	29.59	**23.02**	3.39	**0.33** [1]
	no	99	16.07	18.29	21.31	**24.14**	26.46	30.47	34.84	**24.09**	3.72	
Incontinence	**yes**	13	19.03	19.64	21.60	**23.44**	25.40	28.96	29.26	**24.00**	3.18	**0.95** [1]
	no	102	16.07	18.08	21.09	**23.83**	26.29	30.40	34.84	**23.93**	3.75	

Table 2: Tumor staging after TURB

All patients	Stage	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
T	**<T2**	63	19.26	20.09	23.38	**25.35**	27.26	30.11	34.69	**25.42**	3.10	**0.74** [2]
	T2	119	16.53	20.56	23.25	**25.56**	27.68	31.89	34.84	**25.61**	3.53	
	T3	43	16.07	20.83	22.99	**24.97**	26.35	30.50	35.10	**25.02**	3.40	
	T4	16	19.40	20.77	23.23	**24.68**	27.59	31.19	32.27	**25.48**	3.56	
G	**G1**	5	18.17	19.11	22.86	**23.44**	25.35	28.33	29.07	**23.78**	3.97	**0.52** [2]
	G2	71	16.53	20.75	23.09	**24.77**	26.73	32.12	36.30	**25.22**	3.51	
	G3	292	16.71	19.65	23.09	**25.25**	27.61	31.33	38.34	**25.40**	3.57	
	G4	24	14.03	16.65	23.57	**26.85**	27.68	30.61	31.53	**25.53**	4.39	

Men	Stage	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
T	**<T2**	52	20.06	21.91	23.91	**25.85**	28.16	30.30	34.69	**26.03**	2.87	**0.60** [2]
	T2	79	20.66	21.05	23.96	**26.09**	28.19	31.89	33.91	**26.11**	3.25	
	T3	32	20.83	21.51	22.99	**25.23**	27.01	31.02	35.10	**25.44**	3.15	
	T4	12	21.23	21.98	23.35	**24.68**	27.42	30.05	30.82	**25.47**	3.01	
G	**G1**	4	18.17	18.87	21.69	**23.15**	24.85	28.22	29.07	**23.38**	4.47	**0.35** [2]
	G2	48	20.34	22.99	24.18	**25.52**	27.12	32.37	36.30	**26.11**	3.11	
	G3	217	17.30	20.98	23.51	**25.54**	27.99	31.60	38.34	**25.85**	3.41	
	G4	16	14.03	19.43	24.57	**27.30**	28.73	31.00	31.53	**24.71**	5.63	

Women	Stage	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
T	**<T2**	11	19.26	19.37	20.12	**23.03**	24.18	26.15	26.95	**22.53**	2.58	**0.31** [2]
	T2	40	16.53	18.30	21.58	**24.81**	27.34	30.88	34.84	**24.62**	3.90	
	T3	11	16.07	17.07	23.29	**24.97**	25.47	27.86	29.59	**23.81**	3.76	
	T4	4	19.40	19.97	22.28	**25.17**	28.39	31.50	32.37	**25.50**	5.50	
G	**G1**	1	25.35	25.35	25.35	25.35	25.35	25.35	25.35	25.35		**0.69** [2]
	G2	23	16.53	19.39	21.25	**22.35**	24.18	27.88	34.84	**23.34**	3.64	
	G3	75	16.71	18.24	21.35	**24.28**	26.23	30.52	32.27	**24.08**	3.70	
	G4	8	16.07	17.42	20.19	**25.79**	27.14	27.35	27.39	**23.70**	4.33	

Table 3a: Results after radical cystectomy

All patients	Value	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
T	**T0**	32	18.17	19.16	22.58	**24.40**	26.98	29.37	30.25	**24.43**	3.23	**0.18** [2]
	Tis	14	22.64	23.08	24.28	**25.31**	26.09	31.81	37.04	**26.06**	3.52	
	T1	50	18.02	20.10	23.44	**26.16**	28.30	32.04	34.69	**26.00**	3.68	
	T2	111	17.94	20.47	23.45	**25.66**	27.63	31.31	36.30	**25.70**	3.35	
	T3	143	16.07	19.23	23.09	**25.22**	27.61	31.51	38.34	**25.38**	3.76	
	T4	62	14.03	19.11	22.66	**24.43**	26.86	30.96	34.84	**24.60**	3.83	
N	**N0**	292	16.71	20.19	23.40	**25.47**	27.77	31.89	38.34	**25.68**	3.62	**0.64** [2]
	N1	32	18.07	19.93	22.93	**25.61**	26.35	31.02	33.57	**25.21**	3.42	
	N2	56	14.03	18.72	23.14	**24.89**	27.44	29.92	34.84	**24.96**	3.71	
M	**M0 / Mx**	391	14.03	19.62	23.08	**25.18**	27.55	31.53	38.34	**25.35**	3.65	**0.25** [1]
	M1	15	20.70	22.21	24.68	**26.83**	27.45	29.74	30.12	**26.12**	2.61	
G	**G0**	13	20.05	21.00	23.63	**24.34**	25.35	28.89	30.25	**24.48**	2.65	**0.58** [2]
	G1	5	19.26	19.98	22.86	**22.86**	26.95	29.47	30.10	**24.41**	4.19	
	G2	57	16.53	20.99	23.44	**25.16**	26.61	30.41	36.30	**25.26**	3.16	
	G3	292	17.30	20.21	23.18	**25.39**	27.70	31.89	38.34	**25.59**	3.60	
	G4	28	14.03	16.29	20.88	**25.21**	27.48	30.55	31.31	**24.24**	4.65	
R	**R0**	348	14.03	19.90	23.09	**25.35**	27.56	31.47	38.34	**25.43**	3.63	**0.57** [1]
	Rx / R1 / R2	60	16.53	19.10	23.17	**24.87**	27.18	30.86	34.84	**25.13**	3.51	
Urinary diversion	**Ileal conduit**	191	14.03	19.51	22.85	**24.82**	27.24	31.28	37.04	**25.07**	3.68	**0.00** [2]
	Ileal neobladder	165	18.02	20.68	24.11	**25.95**	28.09	31.82	38.34	**26.08**	3.36	
	Others	47	16.71	18.04	22.90	**19.53**	25.70	29.87	32.11	**24.05**	3.46	

Table 3b: Results after radical cystectomy

Men	Value	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
T	**T0**	25	18.17	20.38	23.63	**24.62**	27.99	29.60	30.25	**25.15**	2.99	**0.29** [2]
	Tis	13	22.64	23.05	24.45	**25.43**	26.12	32.22	37.04	**26.20**	3.62	
	T1	42	18.02	21.78	24.56	**26.38**	28.64	32.10	34.69	**26.56**	3.58	
	T2	80	20.66	21.46	23.71	**25.85**	27.85	31.37	36.30	**26.06**	3.20	
	T3	96	17.30	21.26	23.51	**25.52**	28.16	31.98	38.34	**26.15**	3.69	
	T4	40	14.03	20.56	23.18	**24.69**	26.84	30.14	32.87	**24.92**	3.34	
N	**N0**	216	18.02	21.44	23.93	**25.68**	28.09	32.14	38.34	**26.21**	3.48	**0.45** [2]
	N1	24	19.88	20.94	23.29	**25.50**	26.56	31.19	33.57	**25.52**	3.34	
	N2	40	14.03	21.03	23.17	**25.51**	27.44	29.87	31.53	**25.20**	3.39	
M	**M0 / Mx**	284	14.03	21.25	23.57	**25.56**	28.01	31.90	38.34	**25.94**	3.46	**0.99** [1]
	M1	8	20.70	21.50	24.17	**25.96**	27.34	29.63	30.12	**25.74**	3.06	
G	**G0**	10	21.63	22.53	23.93	**24.48**	25.47	29.23	30.25	**25.14**	2.41	**0.90** [2]
	G1	2	22.86	23.22	24.67	**26.48**	28.29	29.74	30.10	**26.48**	5.12	
	G2	44	21.56	22.99	23.90	**25.36**	26.84	31.12	36.30	**25.85**	2.89	
	G3	208	17.30	20.92	23.65	**25.61**	28.09	32.05	38.34	**26.03**	3.52	
	G4	19	14.03	19.30	23.81	**27.14**	28.41	30.87	31.31	**25.61**	4.26	
R	**R0**	257	14.03	20.98	23.51	**25.61**	28.04	31.98	38.34	**25.96**	3.53	**0.93** [1]
	Rx / R1 / R2	36	20.70	21.85	24.05	**25.69**	27.44	30.60	31.53	**25.88**	2.74	
Urinary diversion	**Ileal conduit**	110	14.03	21.49	23.26	**25.30**	27.62	31.91	37.04	**25.80**	3.55	**0.05** [2]
	Ileal neobladder	148	18.02	20.92	24.21	**26.03**	28.14	31.76	38.34	**26.21**	3.34	
	Others	31	17.30	19.78	23.31	**24.22**	26.47	29.62	32.11	**24.74**	3.05	

Table 3c: Results after radical cystectomy

Women	Value	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
T	**T0**	32	18.17	19.16	22.58	**24.40**	26.98	29.37	30.25	**24.43**	3.23	**0.18** [2]
	Tis	14	22.64	23.08	24.28	**25.31**	26.09	31.81	37.04	**26.06**	3.52	
	T1	50	18.02	20.10	23.44	**26.16**	28.30	32.04	34.69	**26.00**	3.68	
	T2	111	17.94	20.47	23.45	**25.66**	27.63	31.31	36.30	**25.70**	3.35	
	T3	143	16.07	19.23	23.09	**25.22**	27.61	31.51	38.34	**25.38**	3.76	
	T4	62	14.03	19.11	22.66	**24.43**	26.86	30.96	34.84	**24.60**	3.83	
N	**N0**	292	16.71	20.19	23.40	**25.47**	27.77	31.89	38.34	**25.68**	3.62	**0.64** [2]
	N1	32	18.07	19.93	22.93	**25.61**	26.35	31.02	33.57	**25.21**	3.42	
	N2	56	14.03	18.72	23.14	**24.89**	27.44	29.92	34.84	**24.96**	3.71	
M	**M0 / Mx**	391	14.03	19.62	23.08	**25.18**	27.55	31.53	38.34	**25.35**	3.65	**0.25** [1]
	M1	15	20.70	22.21	24.68	**26.83**	27.45	29.74	30.12	**26.12**	2.61	
G	**G0**	13	20.05	21.00	23.63	**24.34**	25.35	28.89	30.25	**24.48**	2.65	**0.58** [2]
	G1	5	19.26	19.98	22.86	**22.86**	26.95	29.47	30.10	**24.41**	4.19	
	G2	57	16.53	20.99	23.44	**25.16**	26.61	30.41	36.30	**25.26**	3.16	
	G3	292	17.30	20.21	23.18	**25.39**	27.70	31.89	38.34	**25.59**	3.60	
	G4	28	14.03	16.29	20.88	**25.21**	27.48	30.55	31.31	**24.24**	4.65	
R	**R0**	348	14.03	19.90	23.09	**25.35**	27.56	31.47	38.34	**25.43**	3.63	**0.57** [1]
	Rx / R1 / R2	60	16.53	19.10	23.17	**24.87**	27.18	30.86	34.84	**25.13**	3.51	
Urinary diversion	**Ileal conduit**	191	14.03	19.51	22.85	**24.82**	27.24	31.28	37.04	**25.07**	3.68	**0.00** [2]
	Ileal neobladder	165	18.02	20.68	24.11	**25.95**	28.09	31.82	38.34	**26.08**	3.36	
	Others	47	16.71	18.04	22.90	**19.53**	25.70	29.87	32.11	**24.05**	3.46	

Table 4a: Early complications I

All patients	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Complications	**yes**	260	18.02	18.58	23.45	**25.65**	27.61	31.74	32.87	**25.51**	3.64	**0.67** [1]
	no	23	14.03	19.05	22.23	**25.83**	28.01	31.57	31.89	**25.14**	4.29	
Cerebral apoplexy	**yes**	3	22.23	22.62	24.17	**26.11**	29.96	33.05	33.82	**27.38**	5.90	**0.63** [1]
	no	195	18.02	19.25	23.42	**25.62**	27.59	31.41	32.87	**25.54**	3.39	
Fistula	**yes**	16	18.03	19.55	23.03	**25.28**	26.18	28.41	29.41	**24.45**	3.14	**0.49** [1]
	no	267	14.03	19.55	23.11	**15.35**	27.42	31.53	36.30	**25.33**	3.54	
Wound-healing disorders	**yes**	24	20.66	20.71	23.09	**25.67**	28.18	34.30	35.10	**26.23**	4.12	**0.37** [1]
	no	259	14.03	19.38	23.11	**25.22**	27.35	31.37	36.30	**25.19**	3.45	
Ileus, gastro-intestinal symptoms	**yes**	48	19.40	20.16	23.69	**25.24**	27.84	31.47	32.11	**25.69**	3.28	**0.40** [1]
	no	235	14.03	19.16	23.05	**25.39**	27.19	31.38	36.30	**25.20**	3.56	
Pulmonary embolism	**yes**	5	20.70	21.49	24.62	**31.31**	31.53	33.36	33.82	**28.40**	5.50	**0.17** [1]
	no	277	14.03	19.58	23.12	**25.35**	27.31	31.29	36.30	**25.25**	3.45	
Hemorrhage, hematoma	**yes**	7	23.41	24.04	25.88	**30.19**	31.44	34.03	35.10	**29.05**	4.11	**0.02** [1]
	no	276	14.03	19.50	23.05	**25.27**	27.28	31.29	36.30	**25.18**	3.45	

Table 4a cont.: Early complications II

All patients	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Anastomosis complications	**yes**	17	18.02	20.92	23.41	**24.97**	26.12	27.59	28.08	**24.50**	2.40	**0.36** [1]
	no	266	14.03	19.55	23.07	**25.42**	27.44	31.53	36.30	**25.33**	3.57	
Hydronephrosis, anuria	**yes**	14	22.04	22.40	24.05	**26.41**	28.65	32.36	32.95	**26.59**	3.34	**0.20** [1]
	no	269	14.03	19.45	23.11	**25.33**	27.31	31.33	36.30	25.21	**3.52**	
Neural impairment	**yes**	5	18.03	19.01	22.94	**24.09**	27.22	28.90	29.32	**24.32**	4.33	**0.65** [1]
	no	278	14.03	19.58	23.13	**25.37**	27.40	31.53	36.30	**25.30**	3.51	
Infections	**yes**	32	16.71	19.64	22.80	**24.44**	26.37	28.70	30.85	**24.46**	3.05	**0.20** [1]
	no	251	14.03	19.56	23.13	**25.40**	27.44	31.71	36.30	**25.38**	3.56	
Cardiovascular complications	**yes**	30	19.92	21.73	23.97	**25.52**	28.40	30.83	33.82	**25.87**	3.26	**0.48** [1]
	no	253	14.03	19.31	23.05	**25.35**	27.31	31.53	36.30	**25.21**	3.54	
Lymphocele	**yes**	14	18.07	19.36	21.95	**26.10**	27.35	31.40	33.82	**25.16**	4.27	**0.98** [1]
	no	269	14.03	19.56	23.12	**25.35**	27.39	31.46	36.30	**25.29**	3.48	
Incontinence	**yes**	16	18.02	18.02	23.21	**27.45**	29.86	33.33	34.69	**26.83**	4.93	**0.10** [1]
	no	267	14.03	19.68	23.05	**25.33**	27.19	31.15	36.30	**25.19**	3.40	

Table 4b: Early complications I

Men	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Complications	**yes**	191	18.02	21.13	23.44	**25.51**	27.46	31.44	36.30	**25.70**	3.18	**0.22** [1]
	no	18	14.03	19.96	25.26	**26.28**	28.31	32.05	32.95	**26.13**	4.18	
Cerebral apoplexy	**yes**	1	33.82	33.82	33.82	33.82	33.82	33.82	33.82	33.82		**0.09** [1]
	no	208	14.03	20.92	23.45	**25.53**	27.50	31.47	36.30	**25.70**	3.22	
Fistula	**yes**	12	20.06	21.08	24.25	**25.58**	26.42	27.90	28.08	**25.08**	2.34	**0.66** [1]
	no	197	14.03	20.98	23.46	**25.53**	27.64	31.60	36.30	**25.78**	3.31	
Wound-healing disorders	**yes**	18	20.66	20.70	21.95	**25.86**	29.37	31.85	35.10	**25.84**	4.26	**0.84** [1]
	no	191	14.03	21.42	23.58	**25.54**	27.53	31.53	36.30	**25.73**	3.17	
Ileus, gastro-intestinal disorders	**yes**	33	20.87	22.44	24.54	**26.29**	28.08	31.42	32.11	**26.39**	2.92	**0.19** [1]
	no	176	14.03	20.76	23.41	**25.51**	27.44	31.62	36.30	**25.62**	3.32	
Pulmonary embolism	**yes**	10	20.70	21.31	23.97	**26.01**	30.67	32.79	33.82	**26.83**	4.42	**0.54** [1]
	no	199	14.03	20.99	23.45	**25.54**	27.47	31.37	36.30	**25.68**	3.20	
Hemorrhage, hematoma	**yes**	7	23.41	24.04	25.88	**30.19**	31.44	34.03	35.10	**29.05**	4.11	**0.03** [1]
	no	202	14.03	20.87	23.45	**25.52**	27.46	31.31	36.30	**25.62**	3.18	

Table 4b cont.: Early complications II

Men	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Anastomosis complications	**yes**	11	18.02	20.33	23.28	**24.07**	26.30	27.77	28.08	**24.38**	2.80	**0.22** [1]
	no	198	14.03	20.99	23.55	**25.56**	27.73	31.59	36.30	**25.81**	3.28	
Hydronephrosis, anuria	**yes**	11	22.04	22.07	22.76	**25.47**	27.76	28.57	28.73	**25.24**	2.65	**0.62** [1]
	no	198	14.03	20.85	23.52	**25.55**	27.55	31.59	36.30	**25.77**	3.30	
Neural impairment	**yes**	3	22.94	23.06	23.52	**24.09**	26.71	28.80	29.32	**25.45**	3.40	**0.75** [1]
	no	206	14.03	20.90	23.47	**25.55**	27.55	31.53	36.30	**25.74**	3.27	
Infections	**yes**	24	20.66	21.55	23.27	**24.61**	26.58	28.96	30.85	**25.01**	2.63	**0.23** [1]
	no	185	14.03	20.89	23.53	**25.61**	27.76	31.82	36.30	**25.83**	3.33	
Cardiovascular complications	**yes**	24	22.05	22.66	24.22	**25.71**	29.10	31.15	33.82	**26.52**	3.14	**0.31** [1]
	no	185	14.03	20.79	23.44	**25.54**	27.46	31.53	36.30	**25.64**	3.27	
Lymphocele	**yes**	10	20.52	20.94	24.05	**26.77**	27.35	32.14	33.82	**26.31**	3.92	**0.57** [1]
	no	199	14.03	20.99	23.45	**25.51**	27.61	31.53	36.30	**25.71**	3.24	
Incontinence	**yes**	12	18.02	20.82	23.21	**27.15**	31.64	33.69	34.69	**27.12**	2.99	**0.28** [1]
	no	197	14.03	20.98	23.51	**25.53**	27.46	31.29	36.30	**25.65**	3.13	

Table 4c: Early complications I

Women	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Complications	**yes**	68	16.53	18.04	21.08	**24.54**	26.39	30.31	34.84	**24.17**	3.91	**0.16** [1]
	no	6	19.03	19.07	19.66	**21.26**	22.74	26.39	27.43	**21.87**	3.14	
Cerebral apoplexy	**ja**	2	22.23	22.42	23.20	**24.17**	25.14	25.91	26.11	**24.17**	2.74	**0.87** [1]
	nein	72	16.53	18.05	21.04	**24.34**	26.39	30.09	34.84	**23.98**	3.92	
Fistula	**ja**	6	18.03	18.04	18.57	**21.76**	25.20	28.50	29.41	**22.47**	4.58	**0.33** [1]
	nein	68	16.53	18.57	21.09	**24.49**	26.39	30.31	34.84	**24.12**	3.83	
Wound-healing disorders	**ja**	6	25.16	25.20	25.36	**25.67**	27.15	33.02	34.84	**27.37**	3.76	**0.05** [1]
	nein	68	16.53	18.04	20.78	**23.94**	26.21	29.52	32.27	**23.68**	3.78	
Ileus, gastro-intestinal disorders	**ja**	15	19.40	19.79	20.70	**24.16**	25.72	30.04	31.89	**24.17**	3.62	**0.98** [1]
	nein	59	16.53	18.02	21.08	**24.46**	26.46	29.70	34.84	**23.94**	3.97	
Pulmonary embolism	**ja**	2	19.92	20.00	20.31	**20.70**	21.08	21.39	21.47	**20.70**	1.09	**0.21** [1]
	nein	72	16.53	18.05	21.08	**24.49**	26.39	30.09	34.84	**24.08**	3.90	
Hemorrhage, hematoma	**ja**	0										
	nein	74	16.53	18.05	21.08	**24.34**	26.28	29.98	34.84	**23.98**	3.88	

Table 4c cont.: Early complications II

Women	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Anastomosis complications	**yes**	4	21.64	22.14	24.14	**25.06**	25.21	25.36	25.39	**24.29**	1.77	**0.89** [1]
	no	70	16.53	18.05	20.97	**24.19**	26.54	30.20	34.84	**23.97**	3.98	
Hydronephrosis, anuria	**yes**	1	31.89	31.89	31.89	31.89	31.89	31.89	31.89	31.89		**0.11** [1]
	no	73	16.53	18.05	21.08	**24.22**	26.18	29.48	34.84	**23.88**	3.80	
Neural impairment	**yes**	2	18.03	18.49	20.32	**22.62**	24.92	26.76	27.22	**22.62**	6.50	**0.71** [1]
	no	72	16.53	18.20	21.08	**24.34**	26.21	30.09	34.84	**24.02**	3.85	
Infections	**yes**	7	16.71	17.42	19.59	**23.50**	25.76	27.12	27.55	**22.64**	4.06	**0.47** [1]
	no	67	16.53	18.14	21.09	**24.46**	26.46	30.37	34.84	**24.12**	3.87	
Cardiovascular complications	**yes**	3	24.22	24.37	24.99	**25.76**	25.93	26.07	26.11	**25.36**	1.01	**0.45** [1]
	no	71	16.53	18.05	21.01	**24.16**	26.46	30.14	34.84	**23.93**	3.95	
Lymphocele	**yes**	3	20.05	20.39	21.74	**23.44**	25.49	27.14	27.55	**23.68**	3.76	**0.93** [1]
	no	71	16.53	18.05	21.08	**24.46**	26.24	30.14	34.84	**24.00**	3.91	
Incontinence	**yes**	4	18.03	19.41	24.96	**28.26**	29.26	29.29	29.30	**25.96**	5.37	**0.23** [1]
	no	70	16.53	18.18	21.08	**24.19**	26.12	30.20	34.84	**23.87**	3.80	

Table 5a: Late complications I

All patients	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Acidosis	**yes**	46	18.73	21.91	23.53	**25.48**	27.42	31.75	36.30	**25.94**	3.42	**0.25** [1]
	no	114	17.94	19.52	22.66	**25.45**	27.38	31.07	32.95	**25.05**	3.48	
Cerebral apoplexy	**yes**	2	18.07	18.36	19.52	**20.98**	22.43	23.60	23.89	**20.98**	4.12	**0.15** [1]
	no	50	18.73	19.54	22.90	**25.14**	28.07	32.01	32.87	**25.42**	3.76	
Leg edema	**yes**	8	21.56	21.58	23.28	**25.85**	27.59	28.25	28.37	**25.32**	2.75	**0.84** [1]
	no	44	18.07	19.14	22.81	**24.55**	28.25	32.08	32.87	**25.24**	4.02	
Gastro-intestinal disorders	**yes**	29	18.02	18.88	23.12	**25.91**	27.55	30.54	32.21	**25.22**	3.48	**0.88** [1]
	no	35	18.07	19.61	22.55	**24.54**	28.23	31.96	32.87	**25.31**	3.96	
Renal failure	**yes**	4	21.63	22.07	23.83	**25.37**	26.20	26.27	26.29	**24.67**	2.17	**0.84** [1]
	no	48	18.07	19.20	22.81	**24.82**	28.16	32.03	32.87	**25.30**	3.95	
Infections	**yes**	16	19.40	20.28	22.65	**24.47**	27.26	30.22	32.87	**24.97**	3.48	**0.71** [1]
	no	38	18.07	19.04	22.96	**24.87**	27.87	32.13	32.87	**25.32**	3.92	
Cardiovascular complications	**yes**	11	19.71	20.32	22.97	**25.78**	27.86	31.87	32.21	**25.57**	4.12	**0.85** [1]
	no	41	18.07	19.10	22.60	**24.57**	28.01	31.89	32.87	**25.16**	3.80	
Stenosis	**yes**	74	17.94	19.25	23.45	**25.40**	27.19	31.39	34.69	**25.49**	3.50	**0.91** [1]
	no	117	14.03	19.55	23.03	**25.61**	27.55	31.04	37.04	**25.38**	3.70	

Table 5a cont.: Late complications II

All patients	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Fistula	**yes**	5	19.40	20.43	24.57	**27.92**	28.73	31.26	31.89	**26.50**	4.75	**0.51** [1]
	no	62	18.02	20.90	23.41	**25.62**	27.69	31.88	32.87	**25.83**	3.58	
Lymphocele	**yes**	4	21.60	22.28	24.99	**26.36**	27.28	28.91	29.32	**25.91**	3.20	**0.85** [1]
	no	63	18.02	19.93	23.42	**25.61**	27.86	31.73	32.87	**25.75**	3.62	
Hernia	**yes**	67	18.31	20.09	22.97	**25.10**	27.42	32.06	35.10	**25.44**	3.60	**0.89** [1]
	no	127	14.03	19.08	23.13	**25.53**	27.47	31.46	37.04	**25.34**	3.75	
Urinary tract infection	**yes**	79	16.53	19.41	23.01	**25.95**	27.57	30.40	34.69	**25.49**	3.59	**0.10** [1]
	no	90	14.03	19.14	22.95	**24.82**	26.62	31.12	36.30	**24.75**	3.62	
Stones	**yes**	17	21.08	22.14	24.46	**26.54**	29.00	33.23	34.69	**26.87**	3.74	**0.08** [1]
	no	122	14.03	19.10	23.11	**25.18**	27.02	30.12	36.30	**24.94**	3.40	

Table 5b: Late complications I

Men	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Acidosis	**yes**	36	18.73	21.75	23.19	**24.94**	26.71	30.42	36.30	**25.35**	3.23	**0.47** [1]
	no	88	18.02	20.92	23.14	**25.85**	28.03	31.76	32.95	**25.68**	3.26	
Cerebral apoplexy	**yes**	1	23.89	23.89	23.89	23.89	23.89	23.89	23.89	23.89		**0.59** [1]
	no	41	18.73	21.56	23.18	**25.91**	28.37	32.11	32.87	**26.02**	3.57	
Leg edema	**yes**	7	21.56	22.25	24.47	**26.59**	27.73	28.26	28.37	**25.85**	2.49	**0.87** [1]
	no	35	18.73	21.31	23.15	**25.18**	29.03	32.14	32.87	**25.99**	3.69	
Gastro-intestinal disorders	**yes**	23	18.02	19.02	23.26	**25.91**	27.59	30.75	32.21	**25.48**	3.50	**0.69** [1]
	no	49	20.57	21.75	23.89	**25.62**	28.09	32.02	37.04	**26.25**	3.42	
Renal failure	**yes**	3	21.63	21.93	23.10	**24.57**	25.43	26.12	26.29	**24.16**	2.35	**0.39** [1]
	no	39	18.73	21.47	23.21	**25.91**	28.55	32.12	32.87	**26.11**	3.60	
Infections	**yes**	14	20.57	21.22	22.95	**24.47**	26.52	30.26	30.52	**25.06**	3.19	**0.17** [1]
	no	58	18.02	21.63	24.04	**26.02**	27.92	32.13	37.04	**26.23**	3.49	
Cardiovascular complications	**yes**	7	22.95	22.96	23.05	**26.37**	29.00	32.01	32.21	**26.52**	3.97	**0.83** [1]
	no	35	18.73	21.27	23.33	**25.18**	28.23	31.96	32.87	**25.86**	3.50	
Stenosis	**yes**	56	18.02	21.23	23.58	**25.55**	27.48	31.70	34.69	**25.86**	3.46	**0.95** [1]
	no	90	14.03	20.93	23.23	**25.91**	27.90	31.41	37.04	**25.77**	3.53	

Table 5b cont.: Late complications II

Men	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Fistula	**yes**	2	28.73	28.89	29.52	**30.31**	31.10	31.73	31.89	**30.31**	2.23	**0.08** [1]
	no	53	18.02	21.59	23.84	**25.62**	27.64	32.15	37.04	**26.10**	3.52	
Lymphocele	**yes**	4	21.60	22.28	24.99	**26.36**	27.28	28.91	29.32	**25.91**	3.20	**0.97** [1]
	no	51	18.02	21.60	23.96	**25.62**	28.05	32.16	37.04	**26.28**	3.61	
Hernia	**yes**	49	19.88	21.42	23.11	**25.88**	28.09	32.17	35.10	**26.00**	3.59	**0.80** [1]
	no	99	14.03	20.79	23.42	**25.61**	27.47	31.57	37.04	**25.68**	3.55	
Urinary tract infection	**yes**	58	18.02	21.41	23.25	**25.79**	27.45	30.15	34.69	**25.64**	3.13	**0.57** [1]
	no	66	14.03	20.26	23.20	**25.34**	27.14	31.46	36.30	**25.33**	3.55	
Stones	**yes**	13	22.41	22.75	25.01	**26.67**	29.00	33.60	34.69	**27.23**	3.60	**0.07** [1]
	no	94	14.03	20.00	23.16	**25.51**	27.05	30.14	36.30	**25.21**	3.34	

Table 5c: Late complications I

Women	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Acidosis	**yes**	11	24.14	24.56	26.06	**27.27**	30.00	33.36	34.84	**28.18**	3.22	**0.00** [1]
	no	27	17.94	18.14	20.51	**23.24**	25.59	28.63	29.41	**23.02**	3.36	
Cerebral apoplexy	**yes**	1	18.07	18.07	18.07	18.07	18.07	18.07	18.07	18.07		**0.12** [1]
	no	9	19.10	19.22	19.71	**21.60**	25.78	28.02	29.24	**22.68**	3.57	
Leg edema	**yes**	1	21.60	21.60	21.60	21.60	21.60	21.60	21.60	21.60		**0.86** [1]
	no	9	18.07	18.48	19.40	**20.94**	25.78	28.02	29.24	**22.29**	3.88	
Gastro-intestinal disorders	**yes**	6	19.10	19.68	21.93	**24.84**	27.20	27.65	27.69	**24.24**	3.51	**0.56** [1]
	no	14	18.03	18.05	19.47	**21.91**	26.90	29.80	30.82	**23.13**	4.42	
Renal failure	**yes**	1	26.18	26.18	26.18	26.18	26.18	26.18	26.18	26.18		**0.22** [1]
	no	9	18.07	18.48	19.40	**20.94**	22.22	27.86	29.24	**21.78**	3.60	
Infections	**yes**	2	19.40	19.89	21.86	**24.32**	26.78	28.75	29.24	**24.32**	6.96	**0.60** [1]
	no	8	19.07	18.43	19.55	**21.27**	23.11	26.04	26.18	**21.70**	2.96	
Cardiovascular complications	**yes**	4	19.71	19.89	20.63	**23.36**	26.65	28.72	29.24	**23.92**	4.41	**0.29** [1]
	no	6	18.07	18.33	19.17	**20.50**	22.07	25.19	26.18	**21.09**	2.94	
Stenosis	**yes**	19	17.94	18.02	23.60	**25.39**	26.64	29.55	30.82	**24.68**	3.48	**0.54** [1]
	no	24	16.53	18.43	20.72	**23.69**	27.23	30.28	31.89	**23.79**	4.15	

Table 5c cont.: Late complications II

Women	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Fistula	**yes**	3	19.40	19.91	21.98	**24.57**	26.24	27.58	27.92	**23.96**	4.29	**0.78** [1]
	no	9	18.03	18.14	21.40	**23.50**	27.55	29.57	30.82	**24.09**	4.49	
Lymphocele	**yes**	0										
	no	12	18.03	18.18	20.90	**24.03**	27.58	29.22	30.82	**24.06**	4.25	
Hernia	**yes**	15	18.31	18.86	21.01	**24.46**	25.74	28.30	30.70	**23.77**	3.43	**0.70** [1]
	no	28	16.53	17.97	20.84	**24.56**	27.40	30.33	31.89	**24.01**	4.16	
Urinary tract infection	**yes**	22	16.53	16.79	21.59	**26.13**	28.85	30.64	32.27	**25.03**	4.58	**0.07** [1]
	no	23	17.94	19.04	20.51	**23.44**	25.06	27.62	31.89	**23.10**	3.43	
Stones	**yes**	4	21.08	21.59	23.62	**24.93**	27.01	30.91	31.89	**25.71**	4.52	**0.65** [1]
	no	28	17.94	18.57	21.05	**24.77**	26.47	28.81	30.70	**24.03**	3.53	

Table 6: Continence

All patients	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Daytime	**yes**	28	16.71	20.67	21.70	**23.64**	27.13	31.50	32.27	**24.42**	3.70	**0.58** [1]
	no	47	18.02	20.07	22.66	**24.34**	26.34	29.87	34.69	**24.73**	3.23	
Nocturnal	**yes**	20	16.71	20.38	22.12	**23.49**	27.13	29.44	32.21	**24.21**	3.53	**0.66** [1]
	no	55	18.02	20.07	21.98	**24.30**	26.51	30.72	34.69	**24.72**	3.43	
Urinary diversion satisfaction	**yes**	104	16.71	19.61	22.34	**24.94**	27.80	332.17	37.04	**25.22**	3.97	**0.46** [1]
	no	5	21.47	21.74	22.83	**23.46**	24.69	26.50	26.95	**23.88**	2.07	

Men	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Daytime	**yes**	16	20.57	20.79	22.48	**24.07**	27.54	30.70	32.21	**25.13**	3.45	**0.70** [1]
	no	37	18.02	19.97	22.60	**24.22**	26.29	30.48	34.69	**24.61**	3.23	
Nocturnal	**yes**	14	20.57	21.15	22.21	**23.49**	26.81	29.32	32.21	**24.47**	3.21	**0.55** [1]
	no	39	18.02	20.01	22.66	**24.34**	26.51	30.36	34.69	**24.90**	3.40	
Urinary diversion satisfaction	**yes**	74	18.02	20.85	23.04	**25.14**	27.73	32.81	37.04	**25.64**	3.78	**0.56** [1]
	no	2	23.46	23.52	23.77	**24.07**	24.38	24.63	24.69	**24.07**	0.87	

Women	yes / no	n	Min	5%	25%	Median	75%	95%	Max	Mean	SD	p-value
Daytime	**yes**	12	16.71	19.11	21.09	**22.28**	25.82	29.43	32.27	**23.48**	3.96	**0.32** [1]
	no	10	20.08	20.47	23.38	**24.74**	28.31	29.27	29.30	**25.18**	3.33	
Nocturnal	**yes**	6	16.71	17.80	21.52	**23.65**	26.44	28.75	29.30	**23.58**	4.47	**0.91** [1]
	no	16	20.08	20.72	21.38	**23.51**	26.20	30.00	32.27	**24.28**	3.59	
Urinary diversion satisfaction	**yes**	30	16.71	18.67	21.08	**23.75**	27.71	31.41	32.27	**24.17**	4.28	**0.95** [1]
	no	3	21.47	21.61	22.15	**22.83**	24.89	26.54	26.95	**23.75**	2.86	

7 Figures

Figure 1: Percentage and number of patients per BMI group

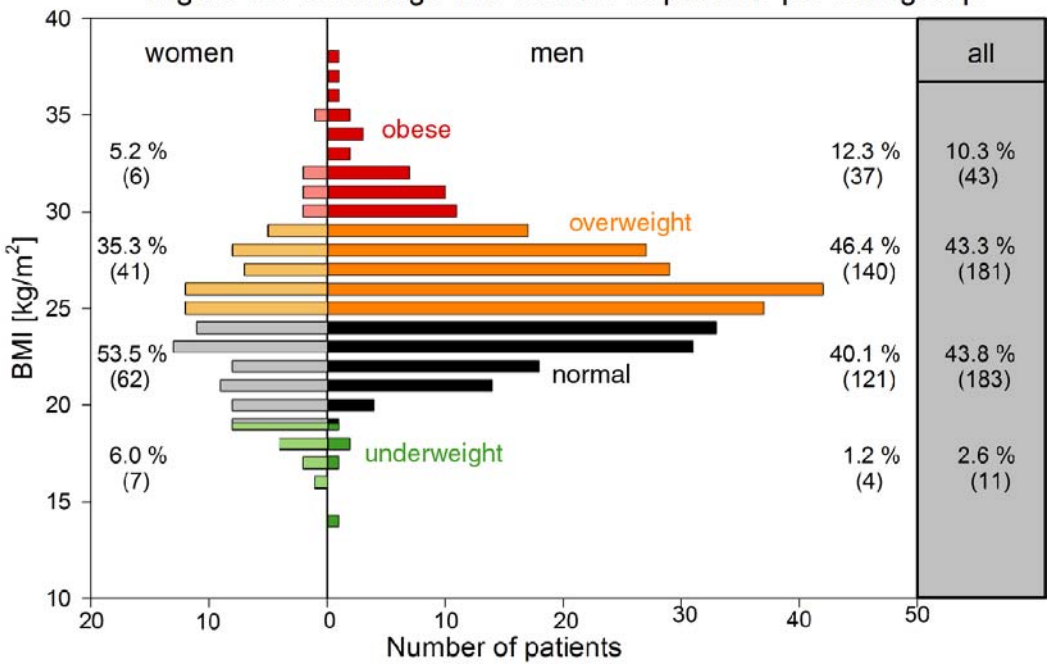


Figure 2: Patient age and BMI distribution

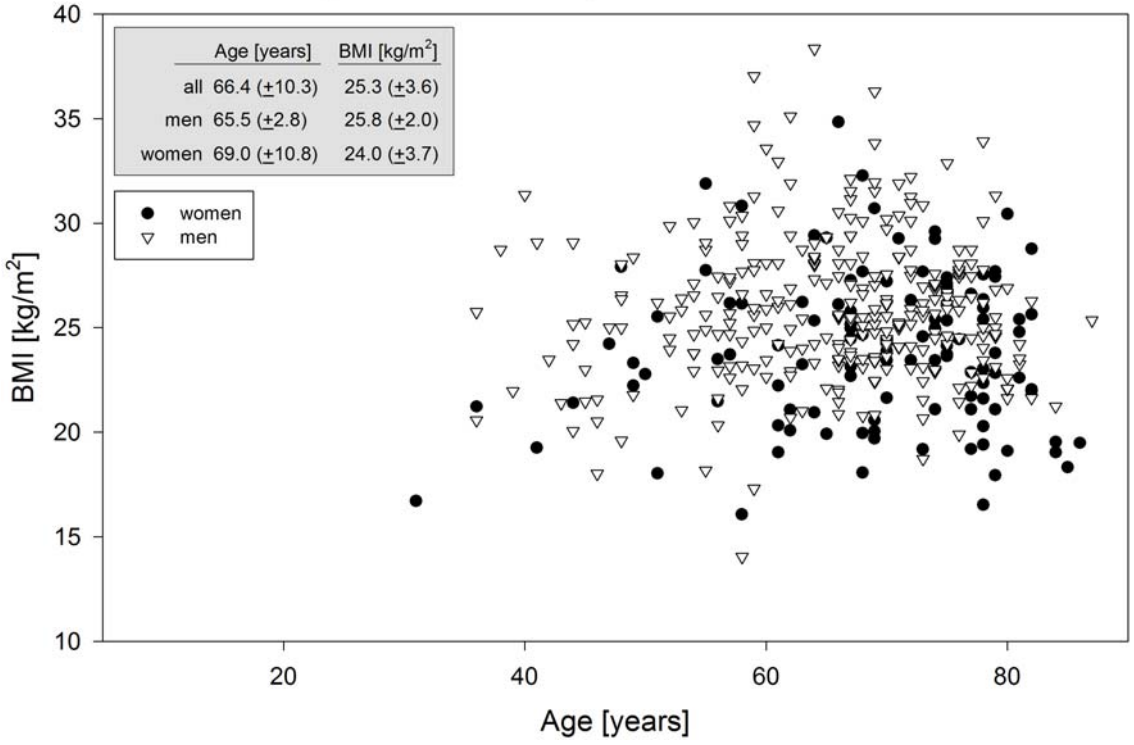


Figure 3: Radical cystectomies per year and BMI group

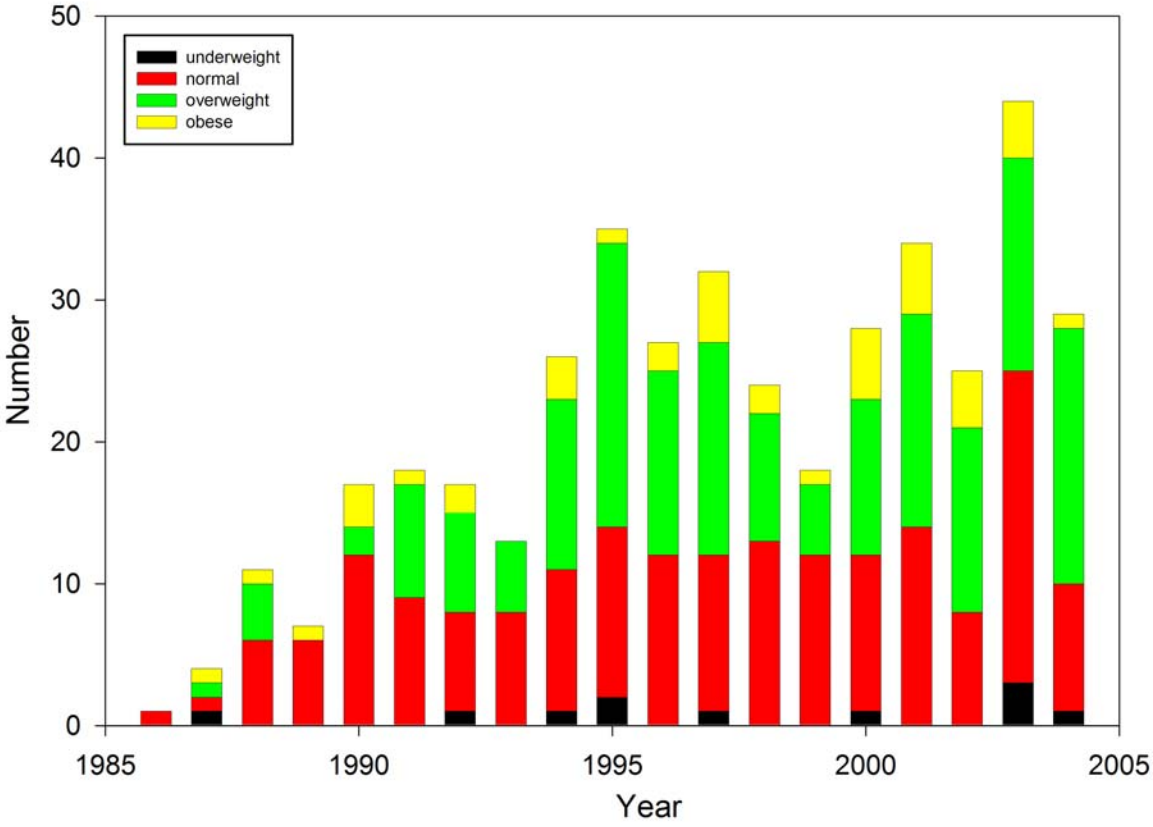


Figure 4: Average duration of radical cystectomies per year

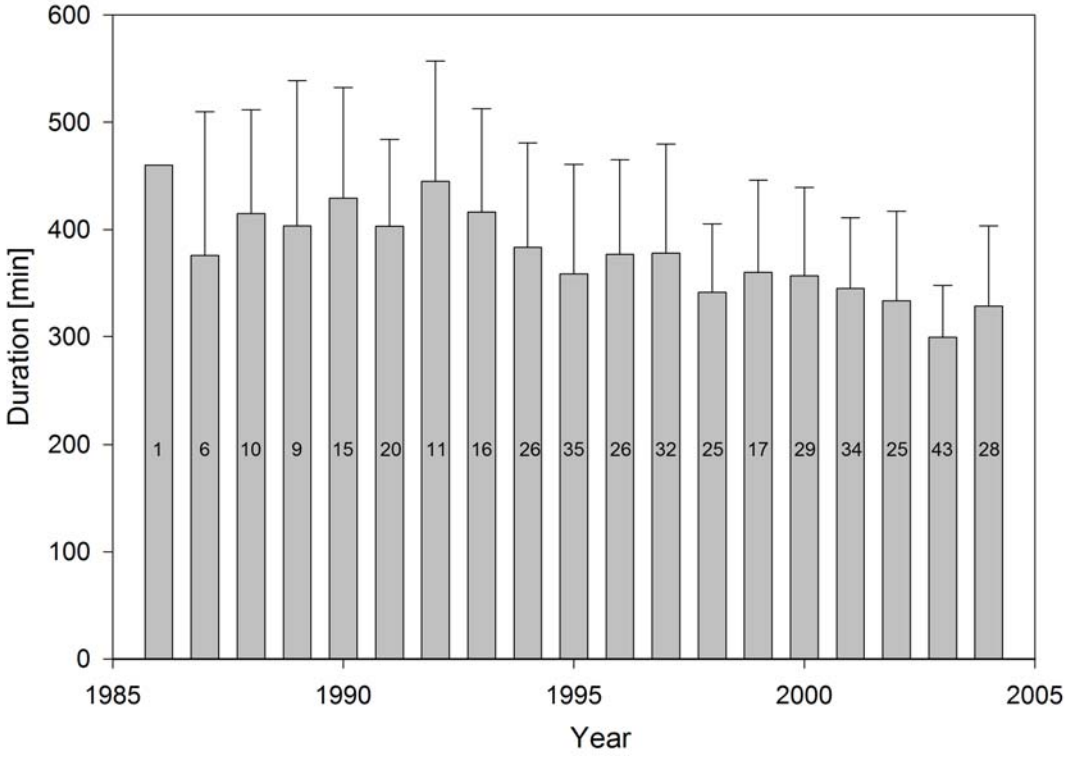


Figure 5: Average duration of radical cystectomies for each BMI group

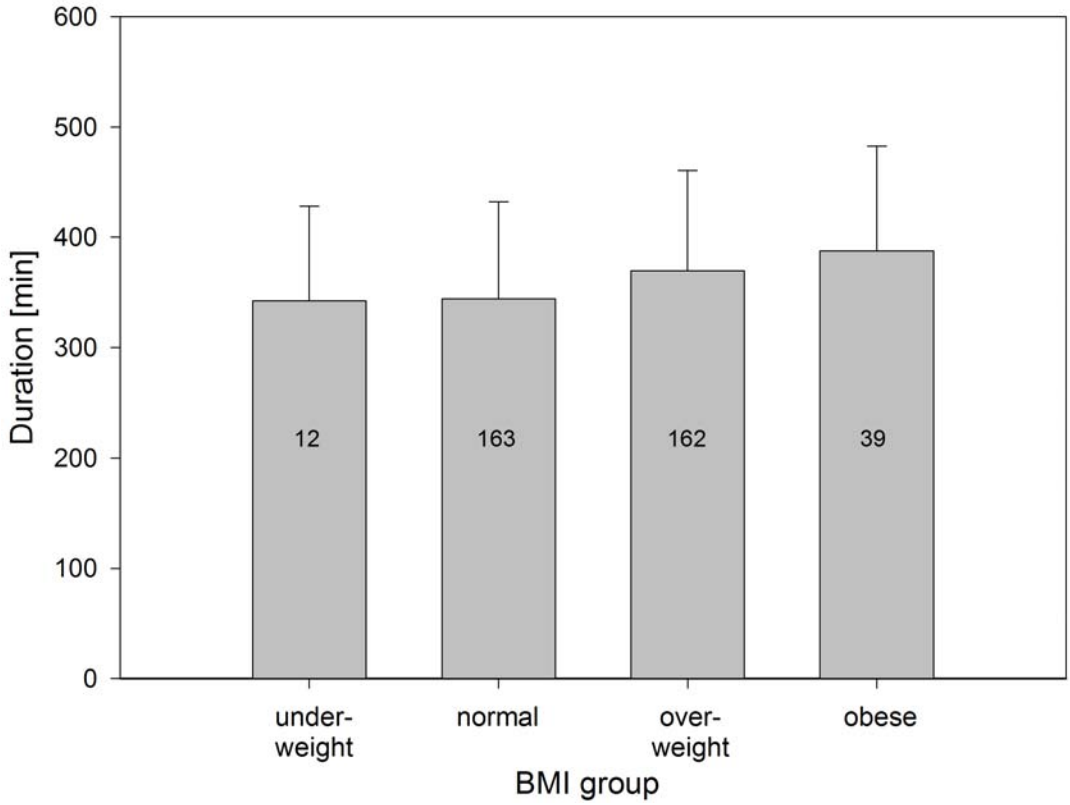


Figure 6: Average duration of radical cystectomies per BMI group in each year

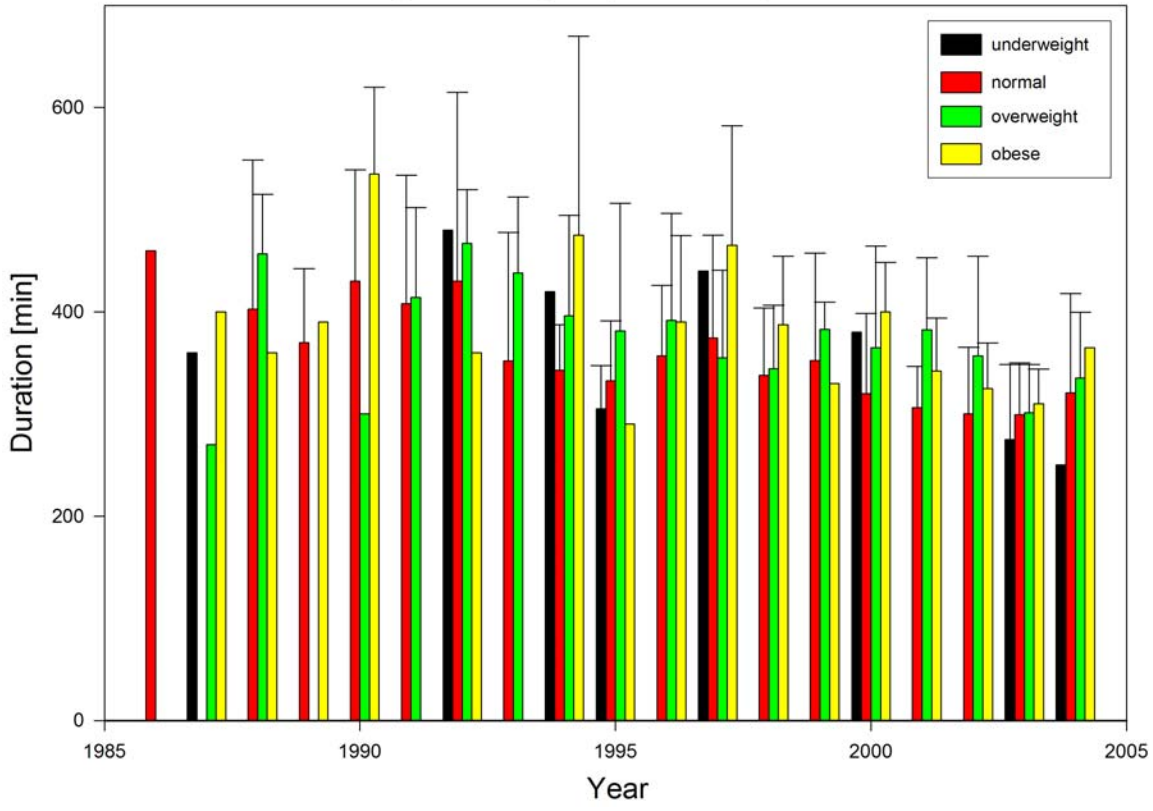


Figure 7: Duration of radical cystectomy dependent on BMI and urinary diversion

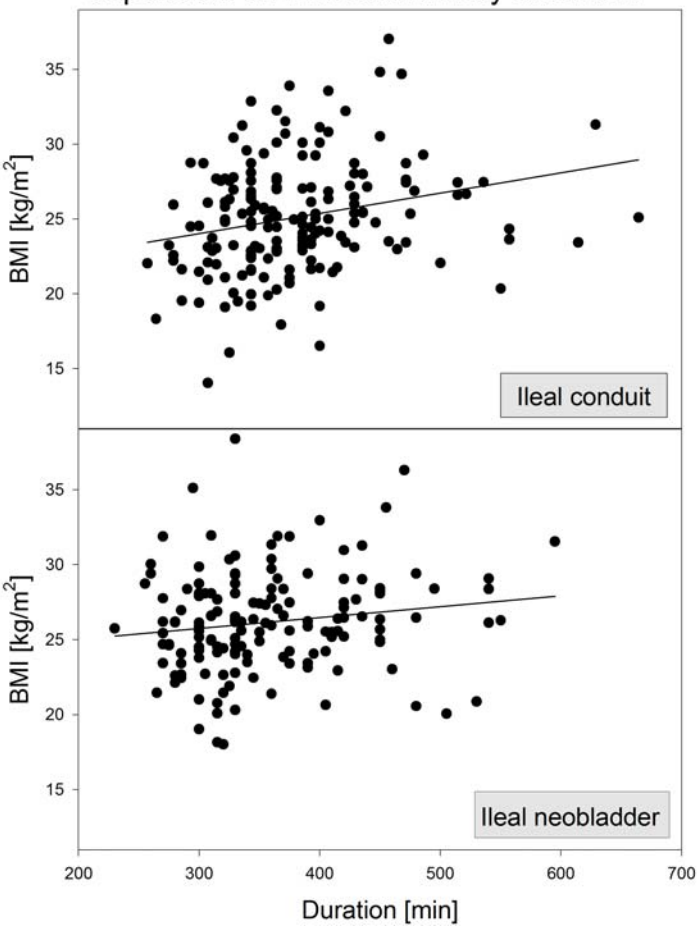


Figure 8: Average duration of radical cystectomy dependent on BMI group and urinary diversion

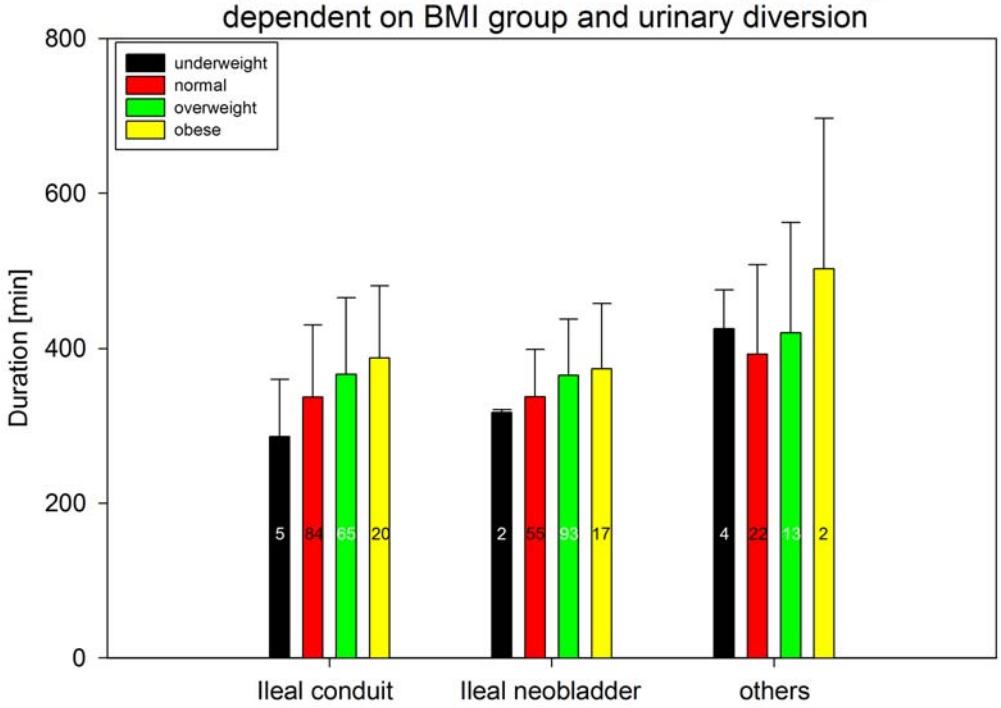


Figure 9: Average rate of erythrocytes transfused during radical cystectomy per year

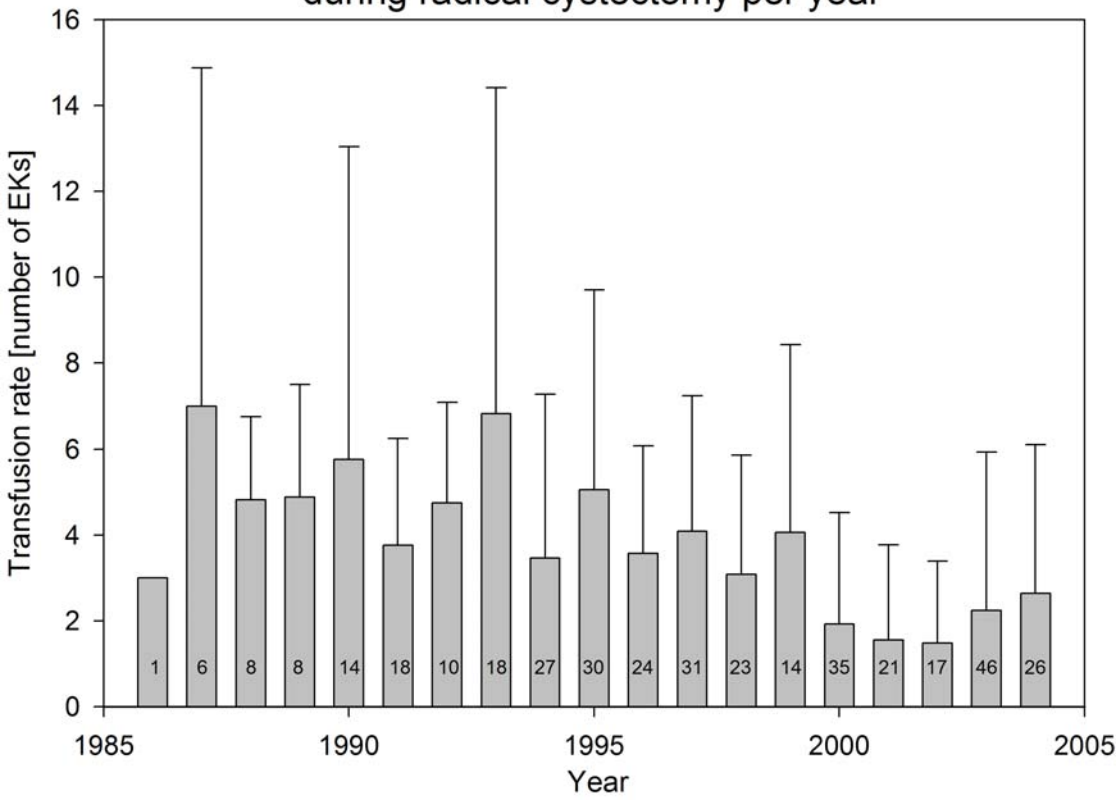


Figure 10: Average rate of erythrocyte concentrates transfused during radical cystectomy per BMI group in each year

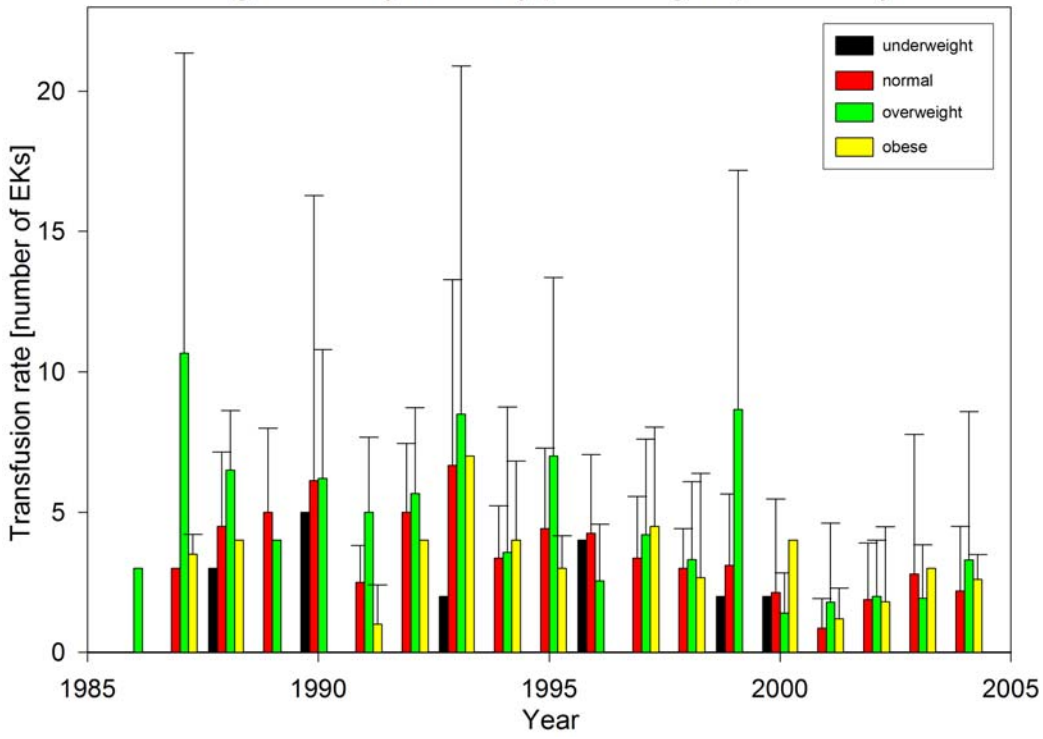


Figure 11: Average rate of erythrocyte concentrates transfused during radical cystectomy in each BMI group

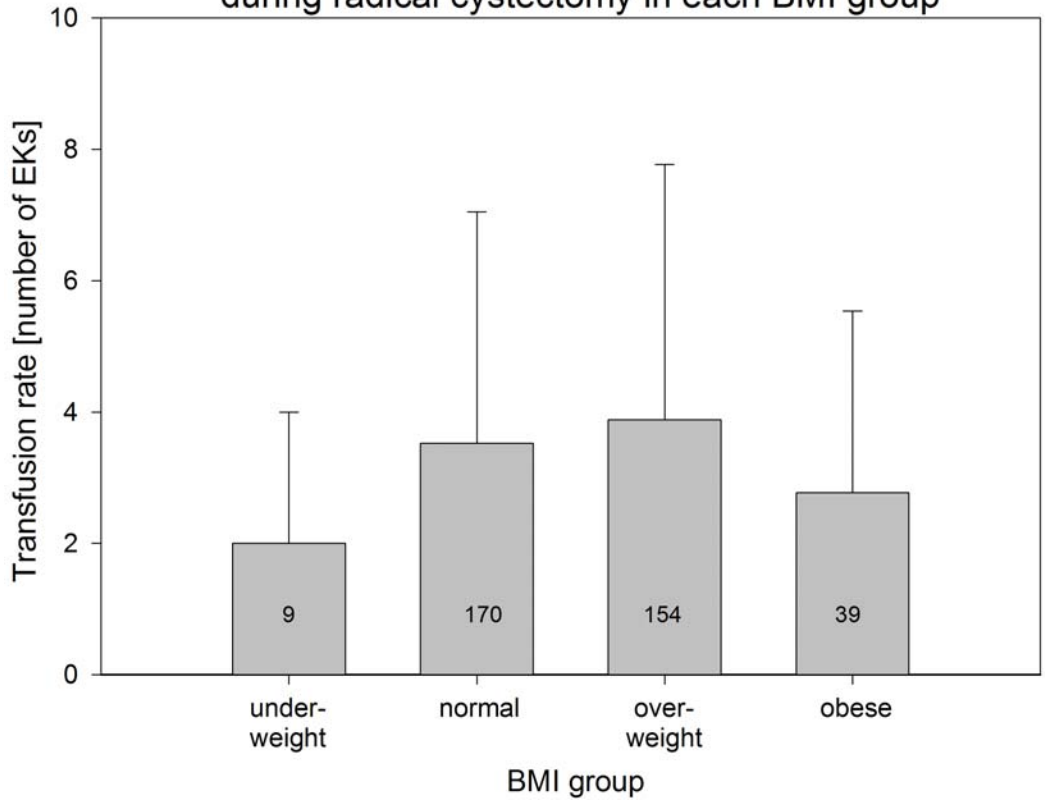


Figure 12: Average rate of erythrocyte concentrates transfused during radical cystectomy dependent on BMI group and urinary diversion

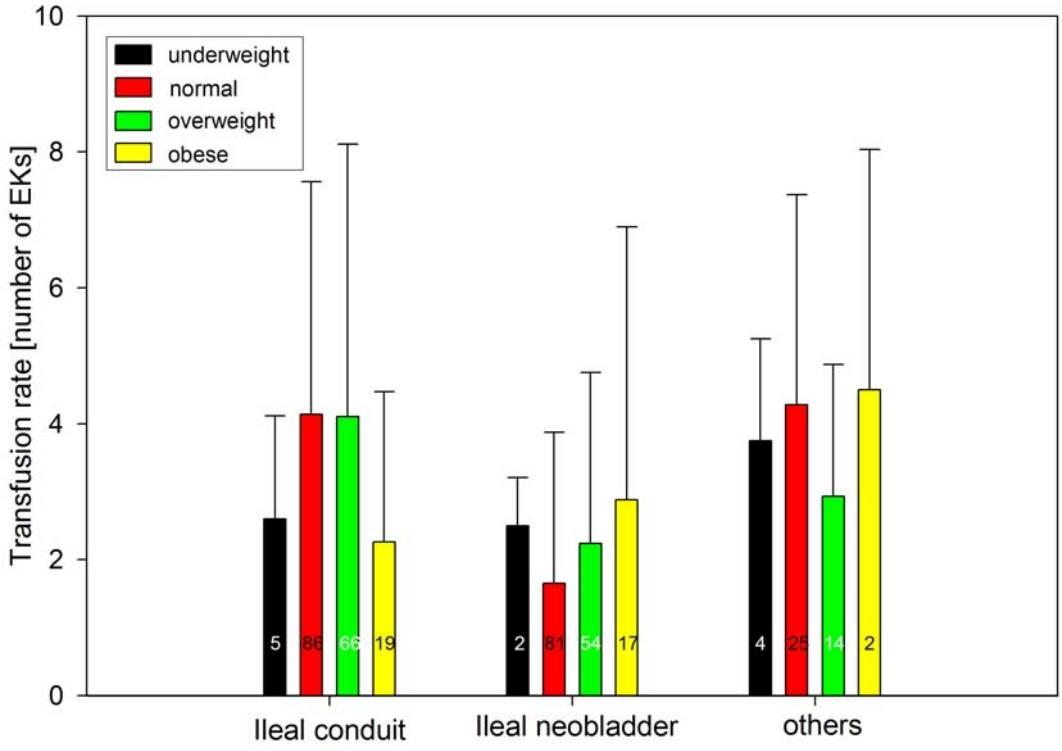


Figure 13: Survival of patients after radical cystectomy per BMI group

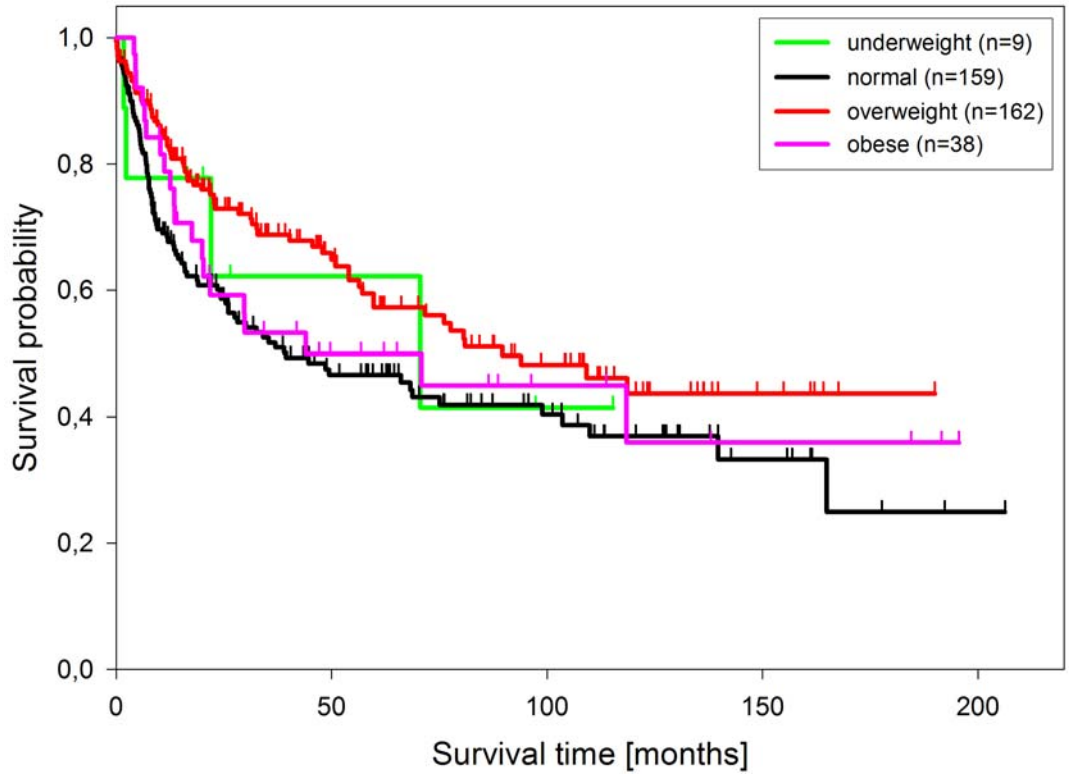


Figure 14: Survival of male patients after radical cystectomy per BMI group

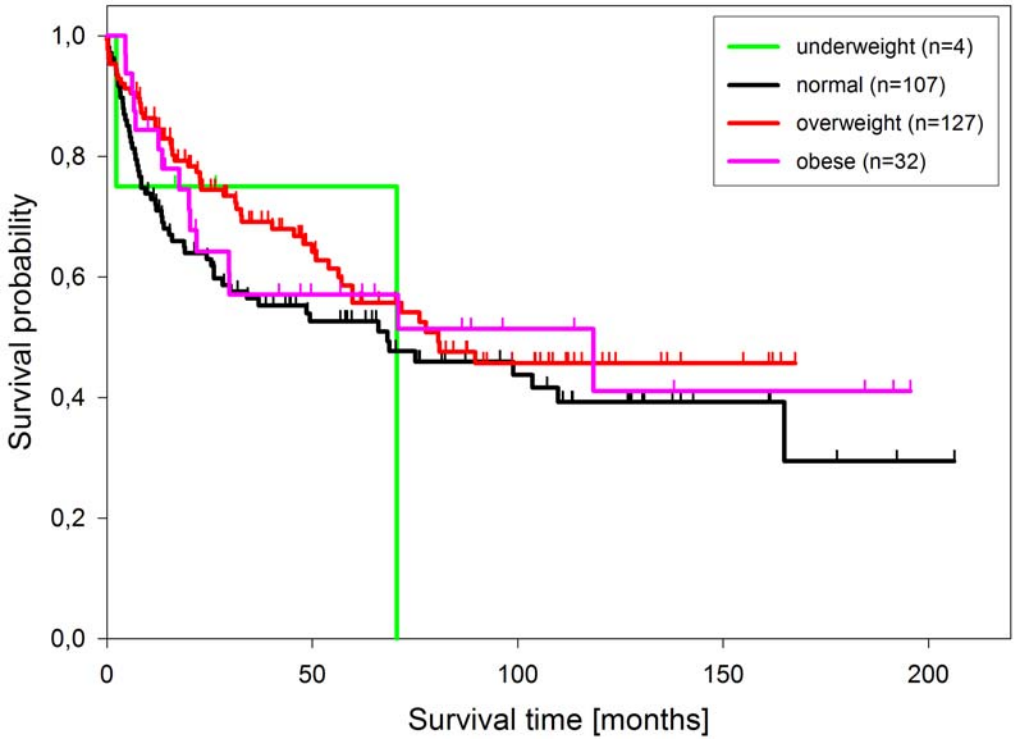


Figure 15: Survival of female patients after radical cystectomy per BMI group

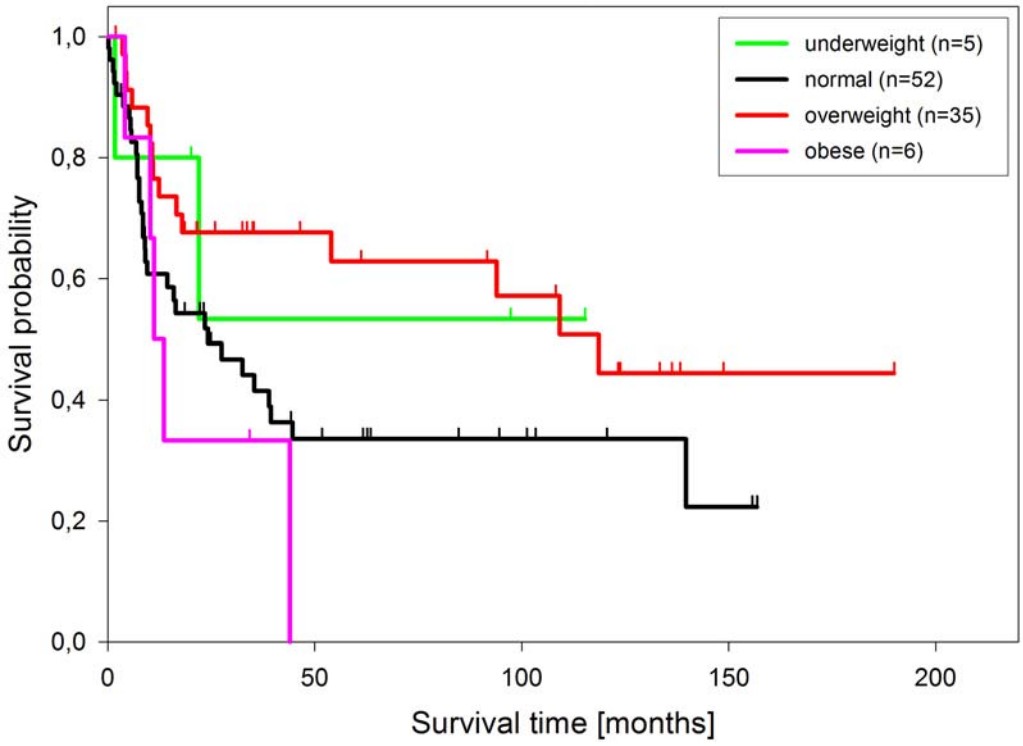


Figure 16: Sex-dependent survival after radical cystectomy

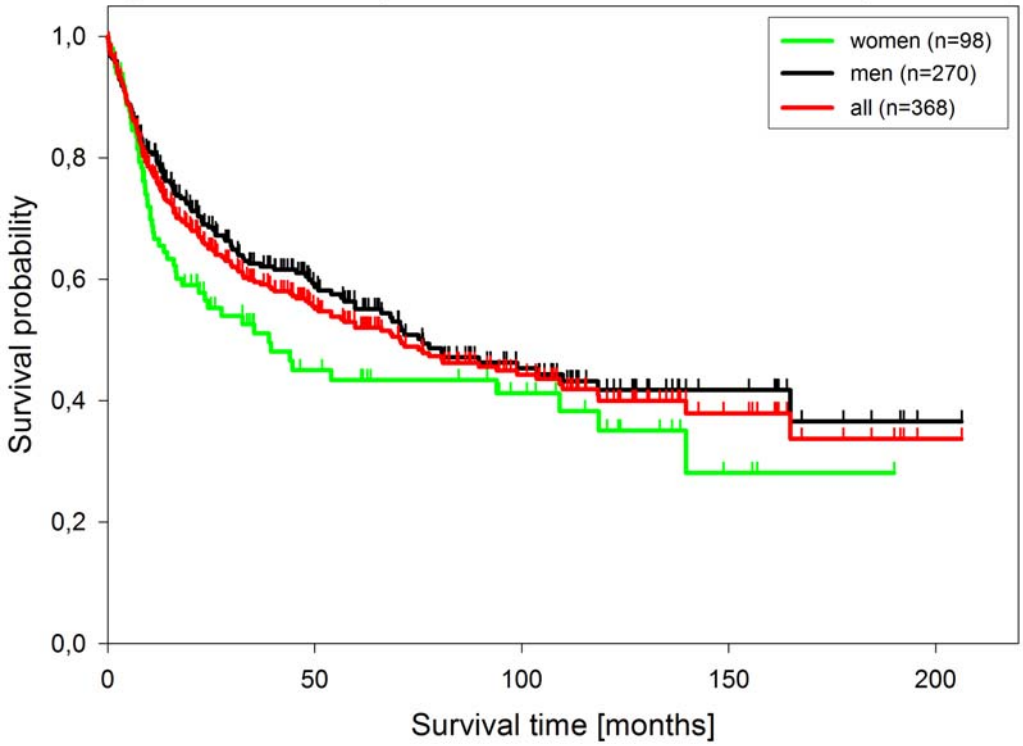


Figure 17: Tumor-related survival after radical cystectomy per BMI group

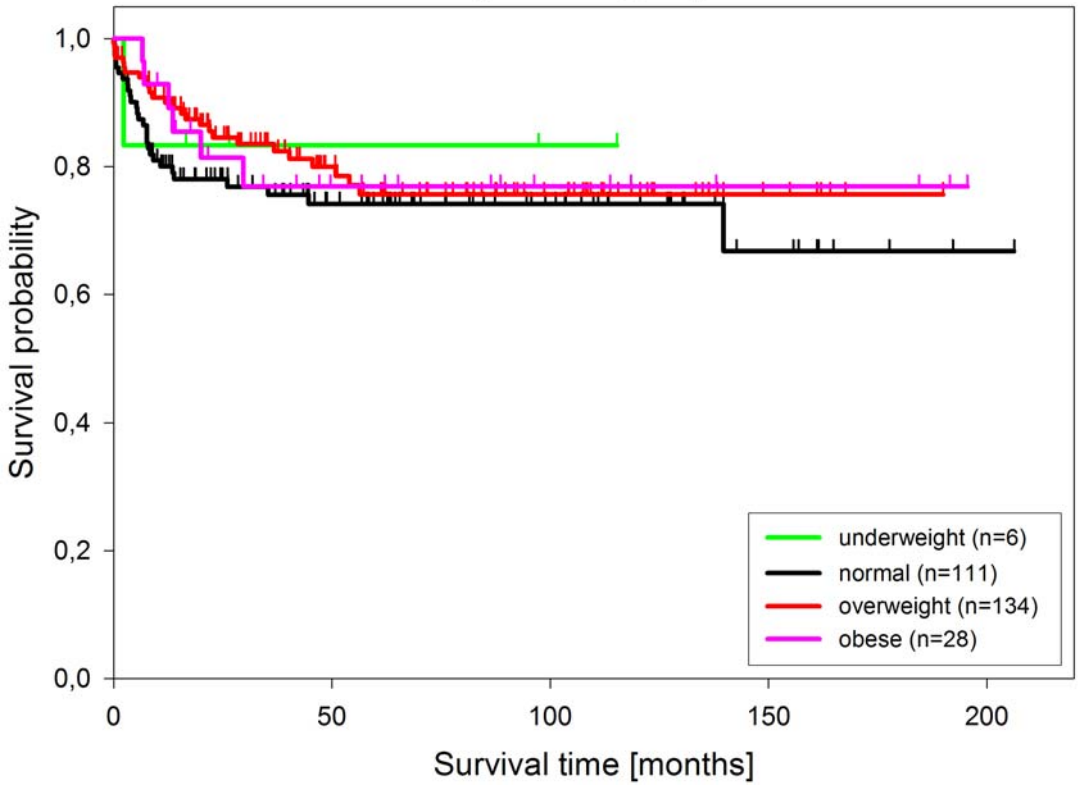


Figure 18: Rate of local tumor relapse after radical cystectomy per BMI group

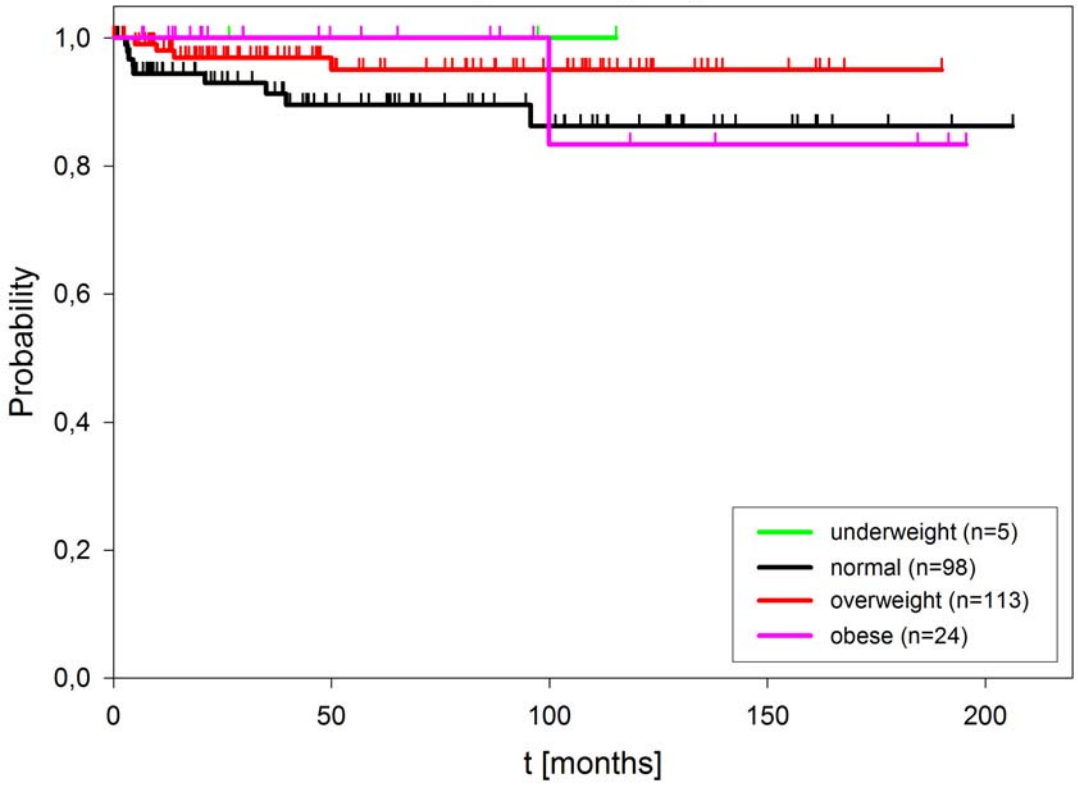


Figure 19: Rate of tumor progression after radical cystectomy per BMI group

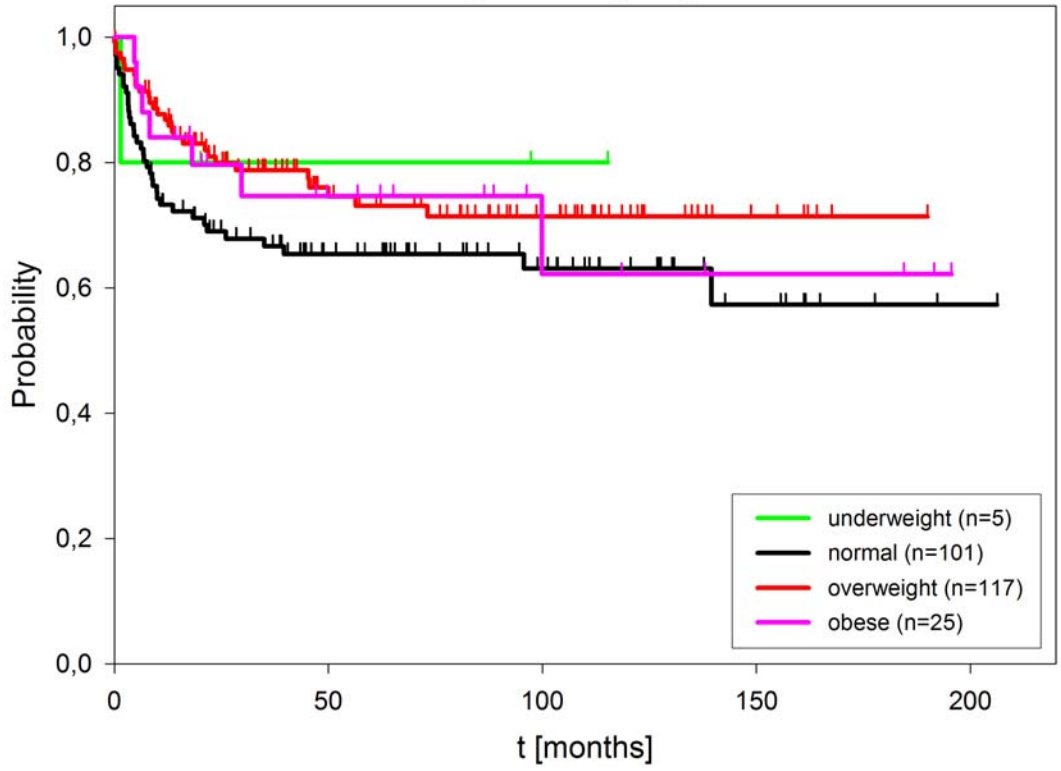


Figure 20: Rate of metastases after radical cystectomy per BMI group

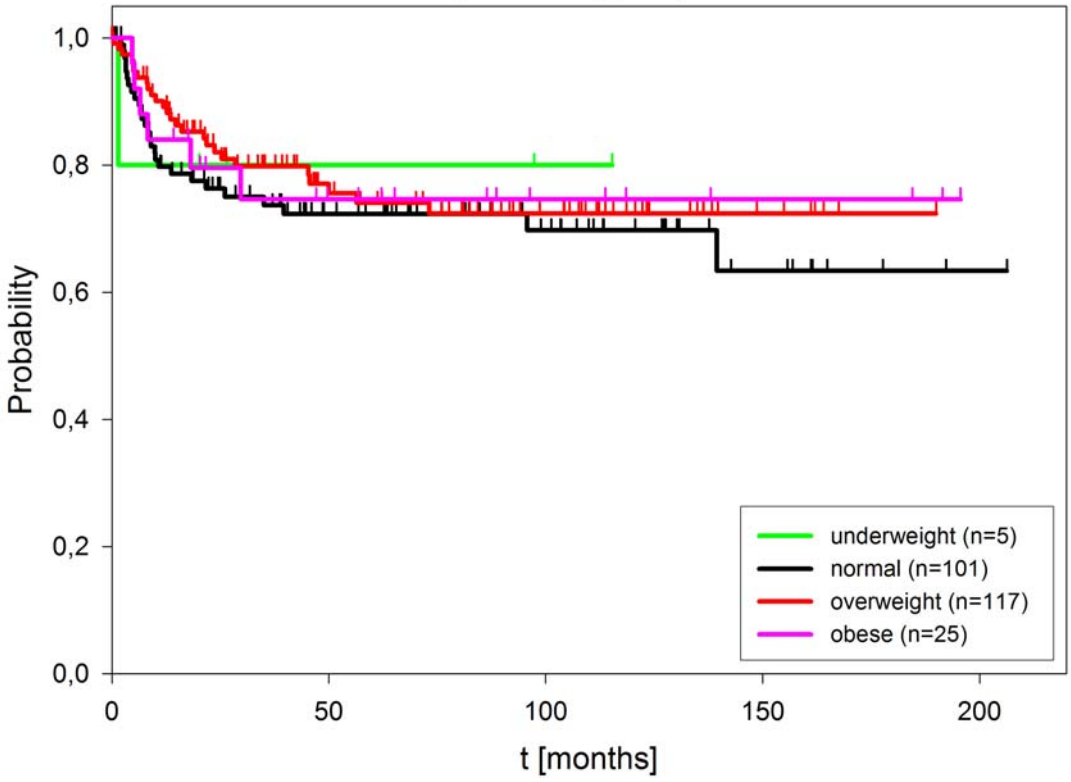


Figure 21: Survival after radical cystectomy dependent on urinary diversion

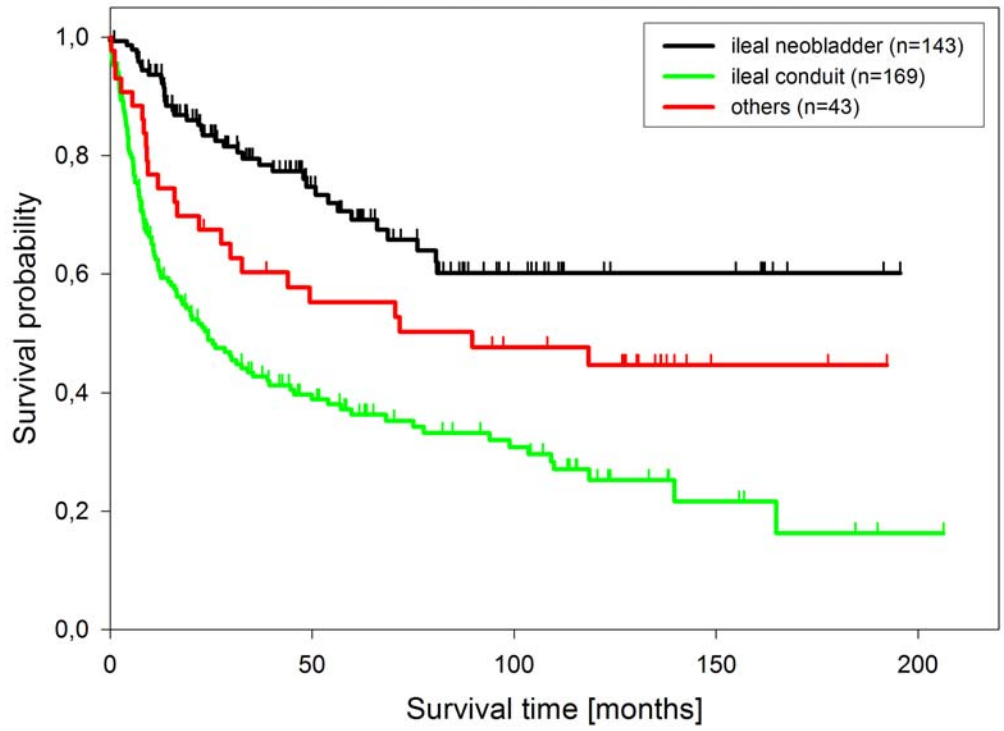


Figure 22: Survival after radical cystectomy and ileal conduit per BMI group

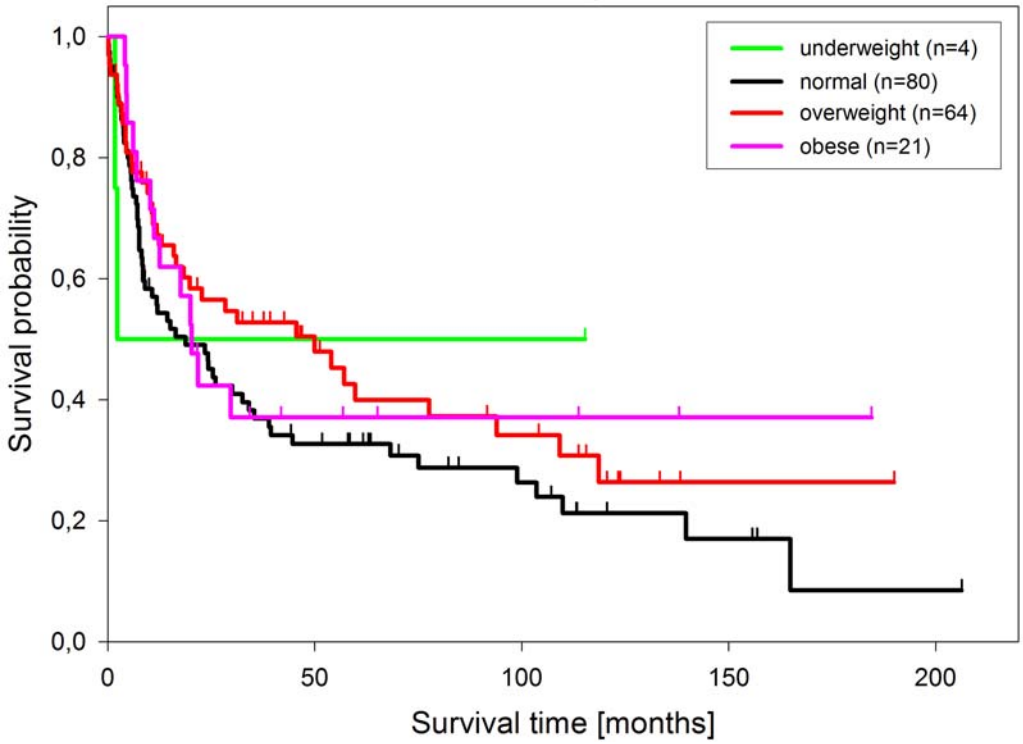


Figure 23: Survival after radical cystectomy and ileal neobladder per BMI group

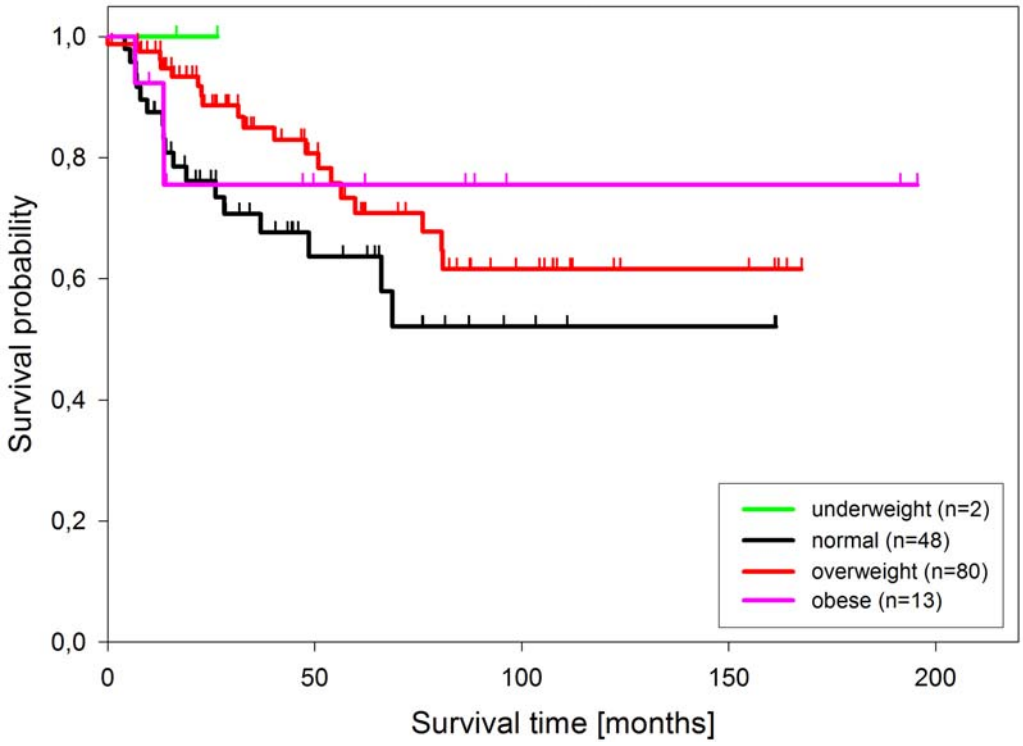
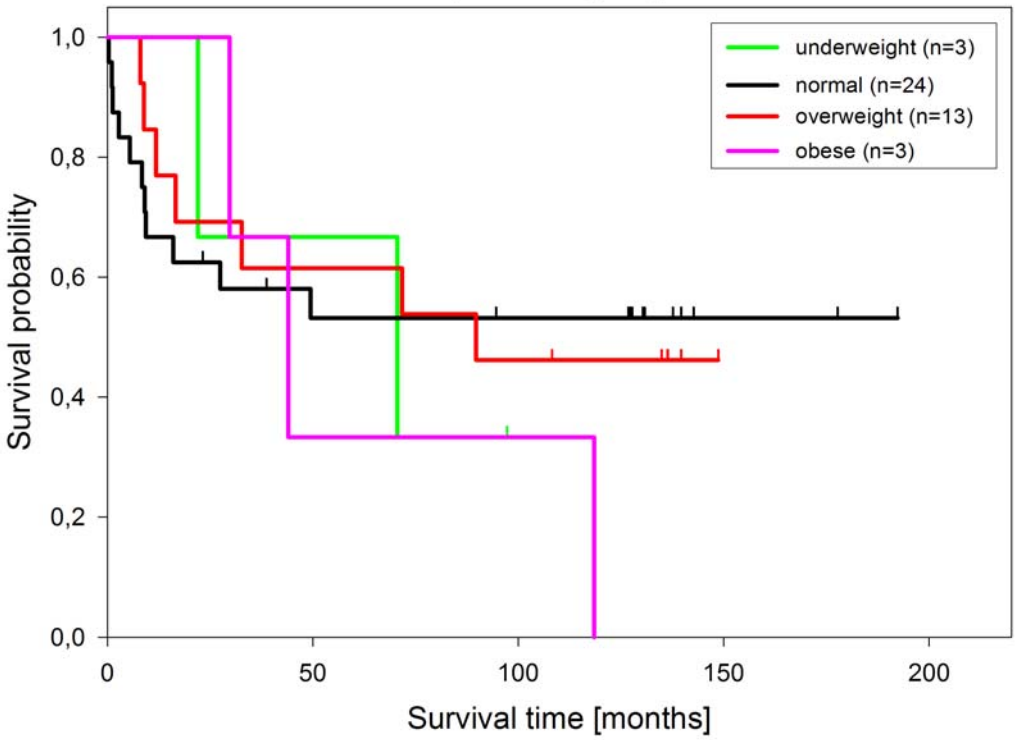


Figure 24: Survival after radical cystectomy and other urinary diversion[1] per BMI group



1: Colon conduit, Hemikock pouch, Indiana pouch, ureterocutaneostomy, ureterosigmoidostomy

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