

THE BENEFITS OF USING CHARLSON COMORBIDITY INDEX IN PREDICTION OF POST OPERATIVE COMPLICATIONS OF RADICAL CYSTECTOMY

Thesis

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Master Degree in **Urology**

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INTRODUCTION

Bladder cancer accounts for 3% of all malignancies. Bladder carcinoma is the most common malignancy of the urinary tract. The worldwide age standardized incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females (*Pleog et al., 2009*). At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer and approximately 30% as muscle-invasive disease (*Vaidya et al., 2001*).

Radical cystoprostatectomy in males and anterior exenteration in females, coupled with en bloc pelvic lymphadenectomy remain the standard surgical approaches to muscle-invasive bladder cancer in the absence of metastatic disease (*Stein et al., 2001*).

Potential complications of radical cystectomy include major and minor morbidity as well as mortality. The morbidity associated with radical cystectomy may be related to the ablative part of the procedure (cystectomy and lymphadenectomy), or complications resulting from use of segments of the gastrointestinal tract for urinary tract reconstruction or diversion after radical cystectomy (*Skinner and Kaufman, 1980*).

Operative mortality for radical cystectomy has been shown to be between 1% and 3% in most modern series. The overall complication rate after radical cystectomy and urinary diversion may be as high as 25% to 35% (*Donat et al., 1999*).

This is a direct result of the fact that bladder cancer patients are more likely to present with significant co-morbidity because of their advanced age at diagnosis and association with cigarette smoking (*Bjerregaard et al., 2006*).

A number of studies have shown a strong correlation between age or co-morbidity and outcomes of radical cystectomy namely a significantly lower rate of progression-free survival for older patients and higher co-morbidity. Elderly and sick patients with advanced disease are often not considered for the most aggressive cancer therapies that are very much recommended for their malignancy. Consequently, the significance of objectively and consistently quantifying co-morbidity is being recognized (*Nilesen et al., 2007*). A plethora of co-morbidity illness scales were found useful in patients' stratification in relation to aggressive treatment tolerance. However, none of such scales was widely integrated into clinical practice to help making aggressive treatment decisions in this subset of older and sicker patients.

The Charlson Co-morbidity Index (CCI) was developed in 1987 based on 1-year mortality data from internal medicine patients admitted to a New York Hospital and was initially validated within a cohort of breast cancer patients. The aim was to evaluate prognosis based on age and co-morbid conditions. It encompasses 19 medical conditions weighted 1-6 with total scores ranging from 0-37 with additional points added for age. With each increased level of the co-morbidity index the cumulative mortality attributable to co-morbid disease increased in a step-wise fashion (*Hall et al., 2004*).

AIM OF THE WORK

To assess the effect of chronic illnesses commonly associated with advanced age on the early outcome of radical cystectomy patients using Charlson Co-morbidity Index to quantify preoperative co-morbidity, also to assess whether a patient will live long enough to benefit from a major surgery like cystectomy.

BLADDER CANCER

Bladder cancer constitutes about 4% of all cancers in west. It is the fourth most common cancer in men as it accounts for about 6.5% of all men cancer. In women it is the ninth most common cancer accounting for about 2.5% of women cancer (*Jemal et al., 2005*).

In Egypt, bladder cancer accounted for up to 33% of malignant tumors registered in 1980 at the registry of the National Cancer Institute in Cairo. According to *Ibrahim and Elsebai (1983)*, it is the most frequent malignancy in males (46% of male malignancy), and ranks after breast cancer in females (16% of female malignancy).

Bladder cancer is generally a disease of middle-aged and elderly people with peak incidence at 7th decade as it is less common in persons younger than the age of 50 years (*Lynch and Cohen, 1995*).

Bladder cancer has a more aggressive variant in elderly people, being relatively at an advanced stage at diagnosis (for both social reasons [patient and medical provider] and biologic reasons [such as impaired host defenses in the elderly]).

Nevertheless, younger patients appear to have a more favorable prognosis because they present more frequently with superficial, low-grade tumors; however, the risk for disease

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progression is the same, grade-for-grade, in younger patients as in older ones (*Wan and Grossman, 1989*).

Bladder cancer has different histological patterns, where in the U.S about 90% is transitional cell carcinoma (TCC) (*Epstein et al., 1998*).

But there is a considerable variation in the pathological patterns noted in different parts of the world. For instance, squamous cell carcinoma (SCC) accounts to as many as 75% in Egypt's bladder cancer statistics (*El-Bolkainy et al., 1981*), but after the early 90s after the era of treatment of bilharziasis and increase smoking the pattern is completely changed, compared to U.S incidence which is less common as it ranged between 3% to 7% (*Hamid et al., 2003*).

About 80% of SCCs in Egypt are associated with chronic infection with schistosoma haematobium. These cancers occur in patients who are, on the average. 10 to 20 years younger than patients with TCC (*Ghoneim and Awad, 1980*).

There are also rare variants of bladder cancer as adenocarcinoma (less than 2% of primary bladder cancers) and urachal carcinoma (*Lynch and Cohen, 1995*).

Table (1): TNM classification (Based on clinical, CT and cystoscopy findings).

<u>Item</u>	<u>Interpretation</u>
<u>Tis</u>	<u>Carcinoma in situ (CIS)</u>
<u>Ta</u>	<u>Non invasive papillary carcinoma tumor</u>
<u>T1</u>	<u>Tumor invades subepithelial connective tissue</u>
<u>T2</u>	<u>Tumor invades, detrusor muscle</u>
<u>T2a</u>	<u>Superficial muscles (inner half)</u>
<u>T2b</u>	<u>Deep muscles (outer half)</u>
<u>T3</u>	<u>Tumor invades perivesical tissues</u>
<u>T3a</u>	<u>Microscopically</u>
<u>T3b</u>	<u>Macroscopic</u>
<u>T4</u>	<u>Tumor invades adjacent organs</u>
<u>T4a</u>	<u>Invasion of the prostate, uterus or vagina</u>
<u>T4b</u>	<u>Invasion of pelvic wall or abdominal wall</u>
<u>Nx</u>	<u>Regional lymph nodes couldn't be assessed</u>
<u>N0</u>	<u>No evidence of spread to lymph nodes</u>
<u>N1</u>	<u>Metastasis in a single lymph node, 2 cm or less in greatest dimension</u>
<u>N2</u>	<u>Metastasis in a single lymph node more than 2 cm but not more than 5 cm in its greatest dimension; or multiple lymph nodes, none more than 5 cm.</u>
<u>N3</u>	<u>Metastasis in a lymph node more than 5 cm in its greatest dimension.</u>
<u>Mx</u>	<u>The presence of distant metastasis couldn't be assed</u>
<u>M0</u>	<u>No evidence of distant metastasis</u>
<u>M1</u>	<u>Distant metastasis.</u>

(Sobin et al., 2009)

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RADICAL CYSTECTOMY

Radical cystectomy is the standard and most definitive form of therapy for high-grade, invasive bladder cancer. Improvement in anesthesia and postoperative management greatly enhanced the outcomes of Radical cystectomy. Also, lower urinary tract reconstruction, particularly orthotopic diversion, has been a major component in enhancing the quality of life of patients requiring cystectomy. The first cystectomy was performed in the late 1800s (*Clark et al., 2005*).

Radical cystectomy is a major surgery and with it significant morbidity may happen. Urologists should be familiar with the prevention, presentation and treatment of the major causes of morbidity and mortality associated with radical cystectomy and lower urinary tract Reconstruction. Complications can be minimized with strict devotion to proper surgical techniques and attention to the perioperative period. Thus, the procedure is complex with the potential for both short-term and long-term complications.

There is abundant evidence that radical cystectomy for bladder malignancies and pelvic exenteration for primary rectal cancer and cervical cancer can lead to meaningful long-term survival. The success of radical cystectomy or pelvic exenteration is highly dependent on good patient selection where an en-block resection may result in prolonged disease-

free survival. Recently the morbidity and mortality of this operation has decreased so that palliative exenteration has a role to help improve quality of life for this difficult group patients (*Buscarini et al., 2007*).

Complications of Radical Cystectomy (*Table 1*).

Radical cystectomy remains associated with significant morbidity and acceptable but notable mortality (*Stein et al., 2009*).

Complications are directly related to the type of urinary diversion, patient age, tumor stage and previous morbidity. The appearance of complications carries a high percentage of long-term complementary medical treatments, or surgical and percutaneous procedures (*Segura et al., 2002*).

Table (2): Complications of radical cystectomy (*Lee et al., 2004*).

Complications	Approximate Incidence (%)
<u>Minor :</u>	
Ileus	12-20
Wound infection	2-7
Pneumonia	2
Mental status change	2
Urinary tract infection	1-3
Cardiac arrhythmia	1-2
Clostridium difficile colitis	1
Acute renal failure	1
Deep venous thrombosis	1
Intraoperative rectal injury	1
Ureterointestinal leakage	1-2
<u>Major:</u>	
Return to operating room	2
Cerebrovascular accident	1
Sepsis	1
Respiratory failure	1
Pulmonary embolus	1
Myocardial infarction	1
Death	1-3

The mortality rate for radical cystectomy is 1% to 2%. The overall complication rate in contemporary series is 25% (*Clark et al., 2005*).

As previously mentioned, the morbidity associated with this surgical procedure falls into three general categories:

1. Complications associated with preexisting co-morbid conditions;

2. Complications stemming from removal of the bladder and adjacent structures, and
3. Complications resulting from use of segments of the gastrointestinal tract for the purpose of urinary tract reconstruction or diversion after radical cystectomy.

Cardiopulmonary disease is relatively common in patients who develop invasive bladder cancer due to association of the disease with advanced age and cigarette smoking. Death from postoperative cardiac arrest is infrequent as it is less than 1% (*Chahal et al., 2003*), but a thorough preoperative evaluation is mandatory in patients, especially those with signs, symptoms, or history of significant cardiac disease before surgery. Postoperative pulmonary embolism is rare (2%) (*Dominguez et al., 2006*).

Early mobilization and, when appropriate, perioperative anticoagulation can minimize the risk of a fatal event to less than 1% (*Malavaud et al., 2001*).

Catastrophic hemorrhage is rare but can occur during cystectomy in 1%. Blood banking and screening for blood-borne pathogens have made transfusion safe for most patients (*Chang et al., 2001*).

Rectal injury occurs in no more than 1% of patients undergoing cystoprostatotomy (*Konety, 2005*).

Bowel obstruction is a potential risk after urinary tract diversion or reconstruction when small or large intestine is

used. Four percent to 10% of patients experience bowel obstruction postoperatively, although less than 10% require operative intervention to correct this problem (**Verleyen et al., 2003**).

Poor blood supply and local sepsis cause ischemia. Drains placed on the anastomosis increase the likelihood of an anastomotic leak, and an anastomosis performed in irradiated bowel is more likely to result in anastomotic failure than one performed in non-irradiated tissue. The importance of careful technique and adherence to the principles is emphasized by the fact that in one series of urinary intestinal diversion, 75% of the lethal complications that occurred in the postoperative period were related to the bowel. Eighty percent of these patients had received radiation before the intestinal surgery (**Mansson et al., 1979**).

Uretero-enteral anastomotic strictures are rare (3%) in non-tunneled anastomosis but are more common when a tunneled anastomosis is performed (**Stein et al., 1996**).

Metabolic disorders, vitamin deficiencies, chronic urinary tract infection, and renal calculus disease occur in varying degrees, depending on the form of reconstruction performed after removal of the lower urinary tract (**Rosario and Anderson, 2000**).

Depression and failure to thrive are common among patients undergoing radical cystectomy. These signs should be actively sought and appropriate intervention provided. The

preoperative prevalence of psychological distress in patients diagnosed with bladder cancer is approximately 45% (*Palapattu et al., 2004*).

Age, co-morbidity and clinical outcomes after radical cystectomy:

Men and women aged >65 years are at high risk for cancers. Data show that persons in this age group have a risk 11 times greater than persons aged <65 years. The impact of advancing age on cancer burden has been examined using data from the National Cancer Institute Surveillance Epidemiology, and End Results (NCI SEER) Program for 1988-1992. This data describes the magnitude of the cancer burden for specific tumors in correlation with age (Fig. 1) (*Yancik, 2000*).

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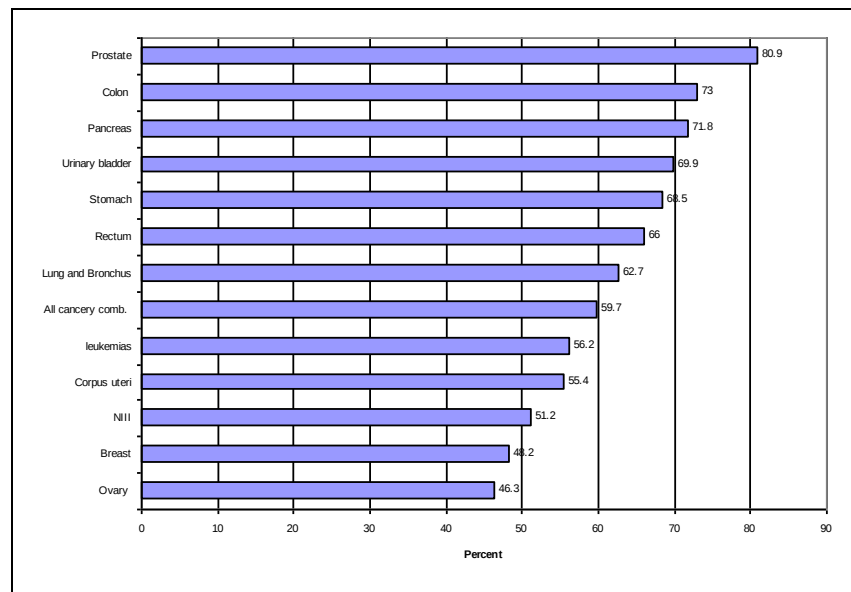


Figure (1): Proportion of persons with selected tumors who are aged 65years.Data from the National Cancer Institute Surveillance. Epidemiology and end results program, 1988-1992. (*Yancik, 2000*).

Improvements in medical care have produced a continuous rise in life expectancy in Europe. In 2025, the proportion of over 65-years-old worldwide will rise from 390 to 800 million and will be around 10% of the total population (**Botterman et al., 2003 and Krege et al., 2004**).

Also, in the U.S life expectancy is increasing. The age shifts within the 65⁺ year age group over time indicate that the old are becoming older. A tremendous expansion of the 75⁺ year age group is anticipated (i.e., the two upper tier age groups combined) [Fig2]. (**National Center for Health Statistics, 1996**).

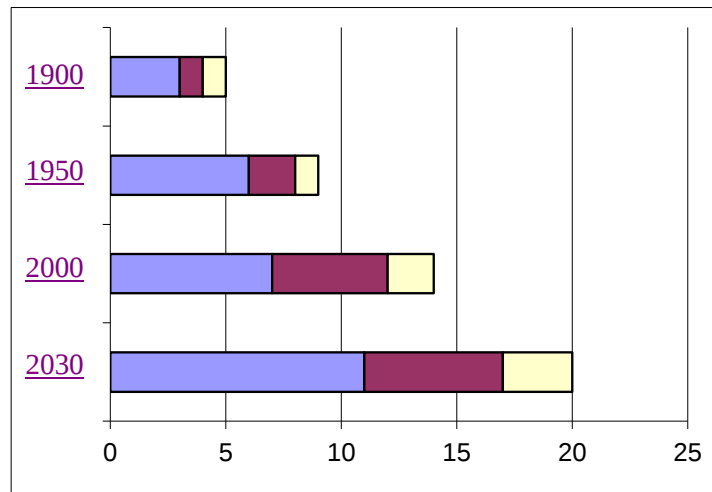


Figure (2): Age shifts over time within the U.S elderly population. Data from the U.S Census Bureau, 1992:1993. ■65-74 years, ■75-84 years, ■ 85⁺ years (**Yancik, 2000**).

The incidence of bladder cancer increases with increasing age with the disease most commonly occurring beyond the 70th year of life (**American Cancer Society Web Site, 2009**).

With around 20-40% of TCCs are of a muscle invasive stage, initially or in progress; standard treatment continues to be radical cystectomy with urinary diversion (**Madeb and Messing, 2004**). Consequently, radical cystectomy in old age will become increasingly important. By comparison, radical cystectomy with urinary diversion is the most invasive surgery in the urogenital tract with accepted perioperative mortality between 1 and 8% (**Quek et al., 2006**).

However, despite that radical cystectomy is the standard treatment for localized or regionally advanced invasive bladder cancer and high risk superficial disease resistant to intravesical therapy, significant improvements in surgical technique, preoperative, preparation, and perioperative care, the complication rate associated with this operation remains high at around 25% (**NCCN Guidelines, 2006 and Shabsigh et al., 2008**).

Consequently, treatment decisions for elderly patients with muscle-invasive or recurrent bladder cancer will constitute an important and difficult clinical challenge in the future (**Dominguez et al., 2006**). Recent data from the surveillance, epidemiology and end results (SEER) database have shown a decreased rate of radical cystectomy in older patients (**Jemal et al., 2005**).

Two possible explanations for these observed differences in the rate of radical cystectomy by age have been proposed: