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Survival Probability of Patients with Bladder Cancer Without Recurrence Following Radical Cystectomy Compared to Remaining Life Expectancy of the Average Danish Citizen

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1. Abstract

1.1 Objectives: To examine whether long-term survival probability of patients with BC undergoing radical cystectomy was different from remaining life expectancy of the average Danish citizen when adjusting for deaths due to BC recurrence.

1.2. Methods: Patients who underwent radical cystectomy between 1992 and 2014 at Aarhus University Hospital were identified through a local database. For the included patients, remaining life expectancy was given by State Bank Denmark. Kaplan-Meier estimates and medians for survival time were calculated.

1.3. Results: We identified 1,354 patients. A total of 816 patients were excluded from the study as they had either died within the first 90 postoperative days or were later diagnosed with recurrence of BC. Thus, 538 patients with at least 4 years of recurrence free survival or death of other known causes were included in the study.

Overall survival of the investigated patient cohort (median 13.54 years; 95% CI 12.43-14.65) was significantly lower than remaining life expectancy for an age and gender matched average Danish citizen (median 15.93 years; 95% CI 15.38-16.48) (p=0,0001).

1.4. Conclusions: Patients with BC undergoing radical cystectomy have a reduced survival probability compared to remaining life expectancy of the average Danish citizen when adjusted for deaths due to BC recurrence.

2. Introduction

Bladder cancer (BC) is among the leading causes of cancer deaths worldwide. Recent reports rank BC as the 10th most common form of cancer [1]. Approximately 1,800 cases of BC are diagnosed annually in Denmark. At the time of diagnosis, about 50% of all bladder tumors are invasive and half of the invasive tumors are also muscle invasive. Muscle invasion is evidence of aggressive tumor with a great tendency to systemic spread and therefore requires particular attention for early radical surgical treatment.

Several risk factors are identified for the development of both non-muscle invasive and muscle invasive BC.

For muscle invasive BC as well as for high risk non-muscle invasive disease, standard treatment is radical cystectomy with bilateral pelvic lymphadenectomy. Due to the major risk of the intervention, patients need to be in a relatively good general condition.

Patients with BC are prone to have comorbidities associated with a etiological factors leading to bladder cancer, mainly smoking which is the main risk factor for development of BC [2]. Frequent comorbidities in this patient group include arteriosclerosis, chronic obstructive lung disease, lung cancer and other malignancies, all known reasons for reduced life expectancy. On the other hand, patients undergoing radical cystectomy are positively selected from more comorbid BC patients because of their assumed ability to un-

dergo major surgery. Moreover, e.g. postoperative follow-up scans potentially act as screening for other diseases which could lead to earlier treatment and thus better prognosis. This study aimed to investigate whether long-term survival probability of patients with BC undergoing radical cystectomy was different from remaining life expectancy of the average Danish citizen when adjusting for deaths due to BC recurrence.

3. Materials and Methods

3.1. Database

A database containing data about all patients who had underwent cystectomy at Aarhus University Hospital was used to obtain the relevant information, including date of surgery, gender, age, follow-up, possible relapse and cause of death. In the period investigated, patients were routinely followed up every 4th to 8th month including CT scan of thorax and abdomen, blood samples and clinical examination for the first 2 postoperative years and yearly thereafter until 5 years.

The database was approved by the Danish Data Protection Agency, and Danish Patient Safety Authority approved the collection of data.

3.2. Patient selection and remaining life expectancy

All patients undergoing radical cystectomy because of BC between 1992 and 2014 were included.

Patients who had either died within the first 90 postoperative days and/or were later diagnosed with recurrence of BC were excluded from the study. Patients were censored at the end of follow-up time or at the time of death with no known recurrence. Event was defined as death for overall survival. For every patient, remaining life expectancy was given by Stat Bank Denmark [3] based on gender, age and year of cystectomy.

3.3. Statistical analysis

The Kaplan-Meier method with log-rank test for significance was used. Data was analyzed in IBM SSPS STATISTICS version 24.

4. Results

In total, 1,354 patients who underwent radical cystectomy between 1992 and 2014 at Aarhus University Hospital were identified in our database. Out of these, 816 patients were excluded from the study as they had either died within the first 90 postoperative days or were diagnosed with later recurrence of BC. Thus, 538 patients with at least 4 years of recurrence free survival or death of other known causes were included in the study The distribution of events and censored observations among the 538 included patients was 194 and 344, respectively.

Overall survival was significantly worse in the observed cohort compared to their remaining life expectancy at the time of surgery ($p<0.01$) (Figure 1).

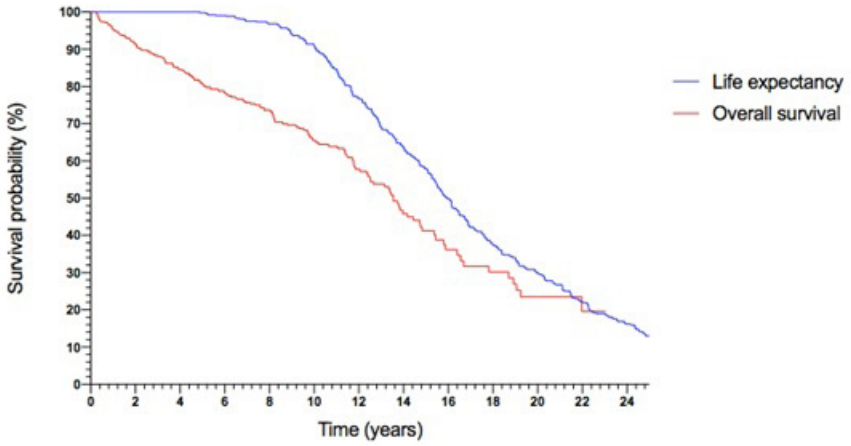

Figure 1: Kaplan-Meier plot illustrating observed overall survival versus life expectancy of a cystectomy cohort without recurrence of bladder cancer

The 50th percentile for overall survival was reached after 13.54 years (95% CI 12.43-14.65), whereas the 50th percentile of remaining life expectancy was reached after 15.93 years (95% CI 15.38-16.48).

5. Discussion

Only few studies have examined the role of comorbidity as an independent prognostic factor for overall survival in BC patients. The excess mortality in patients with BC undergoing radical cystectomy even in absence of recurrence in the present study is likely to be explained by predominant comorbidity of the average BC patient.

Lund et al. examined the prevalence of comorbidity among invasive bladder cancer patients, and the effect of comorbidity on survival and mortality in Northern Denmark. They identified 3,997 patients with invasive bladder cancer among whom 43% had comorbidities. They computed Charlson Comorbidity Index scores

(0, 1-2, 3+) for the patients and computed absolute survival and relative mortality estimates according to comorbidity level. They found that 3- and 5-year mortality rates were higher for patients with comorbidity, with mortality rates more than 2-fold higher among those with scores of 3+ and 1.5-fold higher among those with scores of 1-2 compared with no comorbidity. Thus, they concluded that severe comorbidity was a predictor of poorer survival [4].

Fairey et. al determined the association between comorbidity and overall survival after radical cystectomy. 518 patients with primary BC were included in the analysis. Comorbidity information was obtained through a medical record review using the comorbidity index "Adult Comorbidity Evaluation 27 instrument" (ACE-27) for use in patients with cancer grading specific diseases. They found that increased comorbidity was independently associated with an increased risk of overall mortality after radical cystectomy [5].

Similarly, Megwalu et al. showed that increased comorbidity was associated with poorer overall survival in a subset analysis of 210 patients with BC treated with radical cystectomy. To determine the degree of comorbidity they used the ACE-27 [6].

On the contrary, Miller et al. used another validated risk adjustment index, the Charlson Index to assess preoperative comorbidity in 106 patients treated with radical cystectomy. They performed bivariate analyses to indicate the level of association between overall survival and several covariates including the Charlson Index. Surprisingly, the Charlson Index was not independently associated with overall survival [7]. The discrepant findings of the studies may be related to differences in study populations and methodology, including the different comorbidity assessments. Miller et al. had a relatively small cohort and furthermore they used the Charlson Index instead of ACE-27, which may explain lack of identification of an association between comorbidity and overall survival.

The presence of increased comorbidity amongst the population of this study is likely to be explained by the well-approved association between cigarette consumption and the development of BC, as smoking is a major risk factor in several medical conditions including pulmonary and cardiovascular diseases, as well as other malignancies [8, 9].

Numerous studies present convincing evidence that smoking is the best-identified and most important risk factor for the development of BC [9].

The proportion of smokers among BC patients varies within study populations. Rink et. al. investigated 1506 BC patients treated with radical cystectomy; out of these 693 (46%) and 517 (34%) were former and current smokers, respectively [10], whereas Augustine et al. investigated smoking-related variables in the development of BC and included 1711 patients; 455 (26%) stated their smoking status as former and 856 (50%) as current smokers [11]. Inconsistence in proportions may simply be due to actual variations in smoking habits, but substantial differences in methodology, e.g. questionnaire and definitions, regarding smoking habits are observed within different studies. Furthermore, smoking habits derived from self-reports tend to be biased towards underestimation [12].

Besides BC, multiple studies summarize the broad range of negative health effects on almost every organ system that cigarette smoke exposure cause; it is presumed to cause at least 18 types of cancer, cardiovascular (e.g. atherosclerosis, coronary heart disease, stroke), pulmonary (e.g. chronic obstructive pulmonary disease) and cerebrovascular diseases among others [8, 13].

5.1. Strengths and Limitations

The strength of this study is that it is based on real life clinical data a broad period from 1992-2014.

Furthermore, a benefit of calculating survival by using the Kaplan-Meier method is the possibility to include censored data.

Conversely, the study also presents several limitations. Firstly, the patients in this study are diagnosed and treated at this specific department of urology, and as previously described, the treatment options and follow-up care varies substantially. This might affect the external validity of the study, i.e. the extent of which the results can be generalized to other populations, e.g. other countries.

Most importantly, detailed valid information regarding cause of death in patients without known recurrence and smoking status in all patients were unfortunately not available in all patients.

6. Conclusion

The present study shows that even though BC patients undergoing radical cystectomy are positively selected from more comorbid patients prior to surgery and due to subsequent follow-up their survival probability is reduced compared to the average Danish citizen. This excess in mortality is true also in absence of BC recurrence. These finding can potentially be explained by a great burden of comorbidity in the average BC patient.

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