European Journal of Cancer 95 (2018) 52–58

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Bladder cancer survival: Women better off in the long run

Bettina Kulle Andreassen [a,*], Tom Kristian Grimsrud [a], Erik Skaaheim Haug [b,c]

[a] Department of Research, Cancer Registry of Norway, PB 5313, Majorstuen, 0304, Oslo, Norway
[b] Department of Urology, Vestfold Hospital Trust, Tønsberg, Norway
[c] Institute of Cancer Genetics and Informatics, Oslo University Hospital, Oslo, Norway

Received 8 February 2018; received in revised form 7 March 2018; accepted 8 March 2018

KEYWORDS
Bladder cancer;
Gender;
Gender difference;
Prognosis;
Survival;
Urothelial cancer

Abstract ***Aim:*** Mortality among patients with bladder cancer is usually reported to be higher for women than men, but how the risk differs and why remain largely unexplained. We also described gender-specific differences in survival for patients with bladder cancer and estimated to what extent they can be explained by differences in T-stage distribution at the first diagnosis.

Methods: The present study comprised all 15,129 new cases of histologically verified invasive and non-invasive urothelial carcinoma of the urinary bladder diagnosed between 1997 and 2011 as registered in the Cancer Registry of Norway. Gender-specific excess mortality risk rates and risk ratios were calculated based on a flexible parametric relative survival model adjusting for T-stage and age, allowing the effect of gender to vary over time. We also present gender-specific relative survival curves for different T-stage patterns adjusted for age.

Results: Risk rates were significantly higher for women than men up to 2 years after bladder cancer diagnosis, particularly for muscle-invasive cancers. Thereafter, risk rates appeared to be higher in men. Adverse T-Stage distribution in women explained half of the unfavourable survival difference in female patients 2 years after diagnosis.

Conclusion: The common view of worse bladder cancer prognosis in women than in men needs to be revised. Norwegian women have a less favourable prognosis solely within the first 2 years after diagnosis, particularly when diagnosed with a muscle-invasive tumour; parts of this discrepancy can be attributed to more severe initial diagnoses in women.

* *Corresponding author.*
E-mail address: b.k.andreassen@kreftregisteret.no (B.K. Andreassen).

https://doi.org/10.1016/j.ejca.2018.03.001

1. Introduction

Gender differences in cancer survival have been examined in many studies [1–6], and for most cancer types, survival is found to be better for women than for men. Possible explanations for this phenomenon were gender-specific biological differences [2,3] and differences in environmental exposures and lifestyle [2], as well as tumour biology, gender hormones and clinical management [4]. In bladder cancer, however, most studies and literature reviews have indicated a worse survival for female patients [7–16].

Recently, several reviews have summarised and interpreted results from published studies on the gender difference in prognosis of bladder cancer [12,17–20]. It is suspected that multiple factors influence the gender-specific prognostic outcome [17]. Different anatomy, delays from the first symptoms to diagnosis in females [18,21], variations in hormone receptors as well as tumour biology and less optimal treatment for women [20] were suggested to play a role in the observed differences. However, even after adjustment for some of these factors, the gender difference in survival remained.

Although there is a widespread perception of a disadvantageous prognosis of female patients with bladder cancer, well-performed analyses of evident key factors are lacking. To our knowledge, studies focussing on gender differences so far did not properly describe how gender-specific risk profiles differ over time. There are also methodological challenges when describing the risk difference in survival between male and female patients with bladder cancer. In many publications, the gender difference is described by the hazard ratio (men versus women) assuming that the hazard ratio is constant throughout follow-up time (proportional hazards assumption).

In this article, we will use data from the Cancer Registry of Norway (CRN) to describe gender-specific differences in survival for patients with bladder cancer and evaluate how the risk ratio between male and female patients with bladder cancer varies over time since diagnosis. We will also estimate to what extent the survival difference between men and women can be explained, by gender differences in T-stage at the first diagnosis.

2. Material and methods

2.1. Patients

Since 1953, the CRN has, compulsory by law, registered virtually all new cancer diagnoses in Norway. The registry receives notifications from three independent sources (clinicians, pathology laboratories and from the Cause of Death Registry). Comparisons with data on diagnoses of hospital discharge and consultations, recorded in The Norwegian Patient Registry, are done for quality control and to ensure completeness [22]. Patients are identified through the unique national personal identification number assigned to all newborns and residents in Norway since 1960.

The present study comprises all new cases of histologically verified invasive and non-invasive urothelial carcinoma of the urinary bladder including papillary tumours and carcinoma in situ, excluding dysplasia, diagnosed between 1997 and 2011 and registered in the CRN. In total, 15,129 patients with bladder cancer were included in this study. Participants were followed up until death, migration or end of follow up on the 19th of April 2017, whichever came first. The total follow-up time was 101,518 person-years with a median follow-up time of 12 years.

Morphology, clinical T-, N- and M-categories and grade were defined, based on the most severe diagnosis within a 4-month window from the initial bladder cancer diagnosis. We grouped the patients based on the available clinical T-, N- and M-categories, morphology and grade information: low- (TaLG) and high-grade (TaHG) non-invasive papillary carcinoma (low-grade: TaG1G2; high-grade: TaG3; World Health Organisation [WHO] 1973 [23]), non-invasive flat carcinoma (Tis), invasive carcinoma (in the connecting tissue, not muscle) (T1) as non–muscle-invasive carcinoma (NMIBC) and muscle-invasive carcinoma (T2-4) (MIBC). Therefore, strictly speaking, not all patients with grade II (WHO 1973) would be low-grade patients after the current definition (WHO 2004).

2.2. Statistical analysis

The CRN internal coding system is not able to distinguish between T1 and MIBC tumours without additional information, which is not always available. Therefore, information on clinical T-stage was missing in 16% (2,369 of 15,129) of the patients in our study. This incompleteness could not be assumed to be missing completely at random because the oldest patients (age > 80) had a significantly higher proportion of T-stage missing (20%) than younger patients (age 65–79, 16%; age 50–64, 11%; age < 50, 10%; $p < 0.001$). Therefore, additional information about morphology, metastases, lymph node status, survival time, status (death or alive), gender and age was used in an ordered logistic regression to predict T-stage for patients with missing values. This was performed by using multiple imputation ('mi' function in STATA) to generate 10 imputed datasets [24,25]. Finally, the method of Rubin [26,27] was used to achieve combined point estimates and confidence intervals from the results of these imputed datasets in all analyses depending on T-stage.

Relative survival compares the observed survival in the bladder cancer patient group to the expected survival of the general Norwegian population. Relative survival was estimated using the age-standardised