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Bladder Cancer

Conditional Survival After Radical Cystectomy for Bladder Cancer: Evidence for a Patient Changing Risk Profile over Time

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Abstract

Background: Standard survival statistics do not take into consideration the changes in the weight of individual variables at subsequent times after the diagnosis and initial treatment of bladder cancer.
Objective: To assess the changes in 5-yr conditional survival (CS) rates after radical cystectomy for bladder cancer and to determine how well-established prognostic factors evolve over time.
Design, setting, and participants: We analyzed data from 8141 patients treated with radical cystectomy at 15 international academic centers between 1979 and 2012.
Interventions: Radical cystectomy and pelvic lymph node dissection.
Outcome measurements and statistical analysis: Conditional cancer-specific survival (CSS) and overall survival (OS) estimates were calculated using the Kaplan-Meier method. The multivariable Cox regression model was used to calculate proportional hazard ratios for the prediction of mortality after stratification by clinical characteristics (age, perioperative chemotherapy status) and pathologic characteristics (pT stage, grade, lymphovascular invasion, pN stage, number of nodes removed, margin status). The median follow-up was 32 mo.
Results and limitations: The 5-yr CSS and OS rates were 67.7% and 57.5%, respectively. Given a 1-, 2-, 3-, 5- and 10-yr survivorship, the 5-yr conditional OS rates improved by +5.6 (60.7%), +8.4 (65.8%), +7.6 (70.8%), +3.0 (72.9%), and +1.9% (74.3%), respectively. The 5-yr conditional CSS rates improved by +5.6 (71.5%), +9.8 (78.5%), +7.9 (84.7%), +7.2 (90.8%), and 5.6% (95.9%), respectively. The 5- and 10-yr CS improvement was

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primarily noted among surviving patients with advanced stage disease. The impact of pathologic parameters on CS estimates decreased over time for both CSS and OS. Findings were confirmed on multivariable analyses. The main limitation was the retrospective design.

Conclusions: CS analysis demonstrates that the patient risk profile changes over time. The risk of mortality decreases with increasing survivorship. The CS rates improve mainly in the case of advanced stage disease. The impact of prognostic pathologic features decreases over time and can disappear for long-term CS.

1. Introduction

The management of muscle-invasive bladder cancer is based on radical cystectomy (RC) with pelvic lymph node dissection [1]. Nevertheless, even after RC, 5-yr overall survival rates were estimated at only 60% in recent series [2–4]. Five-year relative survival statistics are often used to measure cancer control and to assess international comparisons. Efforts have been made to better individualize patient prognosis [5,6]. Nevertheless, the probabilities of recurrence and death evolve over time given that these risks are higher in the first years of follow-up.

Cancer prognosis assessed at the time of surgical treatment provides a static view of risk without postoperative follow-up information and does not continue to define individual prognosis accurately and to take into account the changing impact of well-known prognostic factors over time. Conditional survival (CS), in contrast, is derived from the concept of conditional probability [7,8]. CS measures the probability that a cancer patient will survive some additional number of years, given that the patient has already survived for a certain number of years. CS analysis integrates patient survivorship and provides better estimates of survival probability at each follow-up time [9]. That might lead to more informative and individualized prognostic information and might be helpful in patient monitoring.

The usefulness of CS analysis was highlighted in large population-based or tumor-specific cohorts of oncology patients [10–15]. Few studies have investigated the relevance of CS in urologic malignancies, however [9,16–19]. Only one series previously assessed CS in RC patients, highlighting the improvement of cancer-specific survival (CSS) after the first 2 yr [9]. However, this series, which analyzed the Surveillance Epidemiology and End Results (SEER) database, had several noted limitations including the exclusion of patients <66 yr of age, the lack of overall survival (OS) analysis, and the risk of overestimation of CSS. Although it has been suggested that the impact of stage reduces and can disappear for long-term CS, this trend has not been thoroughly assessed in surgically treated bladder cancer [13].

The aim of the present study was to evaluate temporal changes in 5-yr CS in a large multicenter cohort and to determine how the predictive value of well-known prognostic factors at the time of RC evolves over time.

2. Materials and methods

2.1. Patient selection and data collection

This 15-center study was approved by the respective institutional review boards and included 8141 patients who underwent RC with bilateral lymph node dissection for bladder cancer between 1979 and 2012. All patients had pathologic documentation of urothelial carcinoma of the bladder, with no evidence of distant metastasis at the time of surgery. Data included clinical characteristics, pathologic features, perioperative chemotherapy status, oncologic follow-up, and death and its underlying cause. All surgical specimens were processed according to standard pathologic procedures. Tumor grade was assigned according to the 2004 World Health Organization grading system. Pathologic stage was reassigned according to the 2002 American Joint Committee on Cancer TNM staging system. Pelvic lymph node dissection was examined grossly, and all lymphoid tissue was submitted for histologic examination. The extent of dissection was at the surgeon's discretion. Positive soft tissue surgical margins were defined as the presence of tumor at inked areas of soft tissue on the RC specimen. Urethral and ureteral margins were not considered positive margins. Lymphovascular invasion was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls. Cause of death was determined by treating physicians by chart review corroborated by death certificates or by death certificates alone.

2.2. Statistics

The estimation of survival probabilities was performed using the Kaplan-Meier method. CSS and overall survival (OS) were assessed. The CS was estimated using the multiplicative law of probability [20]. That is, the 5-yr CS represents the probability of surviving an additional 5 yr, given that the person has already survived x years (x = time elapsed since RC). For example, for a patient who is alive after 3-yr follow-up, the 5-yr CS rate is calculated by using the 8-yr survival rate divided by the 3-yr survival rate [9].

Patient survival was computed from the day of surgery until the most recent follow-up visit or until death. Variables significantly related to patient survival at Kaplan-Meier analysis were used for the 5-yr CS calculation. Survival rates were then compared with the log-rank test and used in the calculation of the 5-yr CS.

The multivariable Cox regression model was used to calculate proportional hazard ratios for the prediction of mortality after stratification by clinical (age, perioperative chemotherapy status) and pathologic characteristics (pT stage, grade, lymphovascular invasion, pN stage, number of nodes removed, margin status). All tests were two sided with a statistical significance limit at $p < 0.05$. Statistical analyses were performed using SPSS v.19.0 software (IBM Corp., Armonk, NY, USA).

3. Results

Table 1 shows the patient characteristics. After a median follow-up of 32 mo, 44% of the patients ($n = 3582$) died including 27% ($n = 2198$) of bladder cancer–related causes. Median time to death was 24.6 mo. The 5-yr CSS and OS rates were 67.7% and 57.5%, respectively.

Table 2 shows the conditional 5-yr OS rates as a function of the length of patient survivorship. Specifically, given a