

Completeness of bladder cancer staging in the Danish Cancer Registry, 2004–2009

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Objective: To investigate the completeness of tumor, node, and metastasis (TNM) staging for invasive bladder cancer in the Danish Cancer Registry (DCR).

Methods: From the DCR, we retrieved data on TNM stage, year of diagnosis, sex, and age of all-incident invasive bladder cancer patients between 2004 and 2009. Data on comorbidity was obtained from the Danish National Patient Register. We estimated the completeness of TNM registration in the DCR overall and stratified the analysis by sex, age, year of cancer diagnosis, and Charlson comorbidity score. Through knowledge of pathophysiology and clinical coding practice, we designed a clinically based algorithm that allowed tumors with certain missing TNM-stage components to be placed in localized, regional, distant, and unknown categories.

Results: The overall completeness of TNM staging for bladder cancer was 44.1% (95% confidence interval [CI]: 42.7–45.5). Completeness decreased from 60.9% (95% CI: 40.6–78.6) in patients aged 0–39 years to 25.5% (95% CI: 23.2–27.9) in patients aged 80 years or older. Among patients with a low level of comorbidity, completeness was 48.4% (95% CI: 46.6–50.3), decreasing to 34.0% (95% CI: 30.4–37.8) among those with a high level of comorbidity. The highest proportion of missing TNM data was found for registration of lymph node metastases. Defining T1 cancer as completely registered, regardless of missing N and M stage, increased TNM-registration completeness to 61.8%. When we applied a clinically based algorithm, only 29.6% of tumors had an unknown stage.

Conclusion: The overall completeness of TNM staging for bladder cancer in the DCR was low, especially with increasing age and high level of comorbidity. Thus, restricting analyses to bladder cancer patients with complete data on stage may produce substantially selected study populations. Careful considerations should thus be made on handling missing data.

Keywords: bladder cancer, TNM stage, completeness, cancer registry, Denmark

Introduction

Bladder cancer is the fourth most prevalent cancer among men and the fifteenth most prevalent cancer among women in developed countries, with 382,660 new cases and 150,282 deaths worldwide in 2008.^{1,2} In Denmark, the standardized incidence rate of bladder cancer (including noninvasive precancerous lesions) is 46/100,000 among men and 14/100,000 among women, accounting for 4%–5% of all cancers. The incidence has been fairly stable over the last decade.³

Information on cancer stage in Danish hospitals and cancer registries is recorded according to The American Joint Committee on Cancer's Tumor, Node and Metastasis (TNM) classification (AJCC-TNM).⁴ A given TNM class reflects the severity and spread of cancer at the time of diagnosis. "T" describes the local extent of the tumor,

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“N” denotes the presence of lymph node metastases, and “M” the presence of distant metastases. TNM staging is essential for the choice of treatment of most cancers and constitutes an important prognostic predictor.⁵

In 2000 and 2005, the Danish Government issued the National Cancer Action Plans, which encompass initiatives to enhance the diagnosis and treatment of cancer to improve cancer survival in general.⁶ As part of these initiatives, it was decided that the Danish Cancer Registry (DCR) should be used as a tool for national health care planning, for monitoring the effect of new initiatives and to facilitate cancer research. The TNM staging of incident cancers has been reported to the DCR since 2004.⁷ Although the DCR constitutes an important data resource in health care monitoring, as well as in clinical and epidemiological research, the completeness of TNM staging has not yet been evaluated. Missing data on TNM stage in the DCR may bias study results if the missing data are not distributed randomly. Therefore, we conducted this study to evaluate the completeness of TNM classification in patients with invasive bladder cancer. To improve our understanding of how the missing data may potentially bias study results, we stratified the results of completeness by sex, calendar period, patient age, and level of comorbidity.

Materials and methods

We performed this study in Denmark, which has a population of about 5.5 million. All residents in Denmark are provided with free, tax-supported medical care. Since 1968, the Danish Civil Registration System has assigned a unique ten-digit personal identification number (CPR-number), encoding date of birth and gender, to all Danish residents.⁸ This number is used in all Danish registries, allowing unambiguous individual-level data linkage.

Ascertainment of patients with bladder cancer

From the DCR, we identified all patients with a primary diagnosis of invasive bladder cancer (according to the *International Classification of Disease, 10th revision* [ICD-10] code C67) between January 1, 2004 and December 31, 2009. Invasive tumors are defined as tumors that have invaded into or beyond the lamina propria of the bladder. Premalignant tumors (Ta and Tis) are not registered under the ICD-10 code C67. From the DCR, we obtained information on date of diagnosis, age, gender, histologic verification of tumor (based on morphology codes in the DCR), and TNM stage. Through knowledge of pathophysiology and clinical coding practice, we designed

a clinically based algorithm that allowed for categorization of tumors with certain missing TNM stage components into localized, regional, distant, and unknown stage (see Appendix). A registration of Tx, Nx, and/or Mx (denoting that information on tumor size, lymph node metastasis, or distant metastases were not available or could not be assessed) was allowed if the available data on T, N, or M provided sufficient and clinical meaningful information to allocate the cancer case to one of the three defined tumor categories. The unknown tumor category included primarily locally advanced tumors (T3 or T4) with unknown N and/or M stage.

The DCR has recorded information on incident cancers in the Danish population since 1943.^{7,9} Information contains personal characteristics, including CPR-number, age at diagnosis, date of death or migration, and tumor characteristics, including cancer diagnosis, topography, and morphology (according to the *International Classification of Diseases for Oncology* [ICD-O]), laterality, stage, and date of diagnosis. Cancer diagnoses have been registered according to, or converted from ICD-O to ICD-10 since 1978. As mentioned, stage has been recorded using the TNM classification since 2004.^{4,7} To prevent double-registration, the DCR does not accept multiple tumors of the same morphology. In general, only invasive neoplasias are regarded as cancer cases in the DCR. However, this does not apply to urinary tract tumors, including bladder tumors, for which precancerous or precursor lesions (ICD-10 codes: D090, D303, and D414) are regarded as a cancer case.¹⁰

Comorbidity data

Data on comorbidity were obtained from the Danish National Patient Registry.¹¹ The registry contains data on all admissions to nonpsychiatric hospitals in Denmark since 1977 and outpatient visits since 1995 and information includes the CPR-number, date of admission or contact, date of discharge, and diagnosis codes. We described preexisting comorbidity using a modified version of the Charlson comorbidity index (CCI), in which each disease category has an associated weight, based on the adjusted risk of 1-year mortality.^{12,13} We generated CCI scores from hospital diagnoses (excluding bladder cancer) within 10 years preceding the date of cancer diagnosis. We computed the following CCI scores: 0 (low), 1–2 (medium), and 3+ (high).

Statistical analysis

We calculated the proportion of complete TNM stage registrations and corresponding 95% confidence intervals (CI), overall, and by each stage category (ie, T, N, and M).

A registration of Tx, Nx or Mx was defined as unknown stage. We stratified completeness by gender, age (0–39 years, 40–59 years, 60–79 years, and ≥ 80 years), year of cancer diagnosis, and CCI score (0, 1–2, 3+). We calculated proportions of histologically verified cancers and repeated all analyses restricted to those (Sub-analysis 1). In another sub-analysis, we categorized the combination T1NxMx as a complete TNM registration (Sub-analysis 2).

Analyses were performed using SAS® (v 9.2; SAS Inc, Cary, NC).

Results

We identified 5178 patients with incident invasive bladder cancer during the study period (2004–2009). Seventy-two percent were men ($n = 3744$) and 28% were women ($n = 1434$). Median age at diagnosis was 72.9 years, without any major gender difference.

Overall completeness of the TNM stage was 44.1% (95% CI: 42.7–45.5) and this was similar among men and women: 44.3% (95% CI: 42.7–45.9) and 43.5% (95% CI: 41.0–46.1), respectively (Table 1). Overall completeness changed marginally when restricting the analysis to histologically verified cancers (44.9%; $n = 4892$ verified cases).

Stage completeness declined with increasing age (Table 1). Only 25.5% (95% CI: 23.2–27.9) of patients aged 80 years and older had a complete registration. This was mainly due to missing assessment of lymph

node (N-completeness = 29.1%) or distant metastases (M-completeness = 35.2%). Stage completeness also declined with increasing level of CCI. Overall completeness of TNM-stage was 48.4% (95% CI: 46.6–50.3) among patients with the lowest CCI score, compared with 34.0% (95% CI: 30.4–37.8) among those with the highest score. Completeness was lowest for presence of lymph node metastasis (N), although with some improvement over time, from 45.7% in 2004 to 50.5% in 2009. Similar tendencies were observed for metastasis (M) and TNM overall, whereas completeness of the T stage declined slightly, from 92.5% in 2004 to 89.8% in 2009.

When classifying the combination T1NxMx as a complete stage registration, overall completeness of TNM stage increased to 61.8% (919 patients changed status from having incomplete to complete registration).

Using the algorithm for localized, regional, and distant disease (Appendix), the proportion of tumors with unknown stage declined to 29.6% (Table 2). Again, patients of older age or with a high level on the CCI had the highest proportion of tumors of unknown stage.

Discussion

In this study on TNM stage completeness for invasive bladder cancer in the DCR, we found that the overall completeness was less than 50%. The proportion of cancer patients with unknown stage increased with increasing age and level

Table 1 Completeness of tumor, node, and metastasis (TNM) registration among bladder cancer patients in the Danish Cancer Registry

	TNM-completeness		T-completeness		N-completeness		M-completeness	
	% (n)	95% CI	% (n)	95% CI	% (n)	95% CI	% (n)	95% CI
Year of diagnosis								
2004	43.1 (387)	39.9–46.4	92.5 (831)	90.7–94.1	45.7 (410)	42.4–48.9	55.5 (498)	52.2–58.7
2005	41.3 (349)	38.0–44.6	91.3 (772)	89.2–93.0	44.6 (377)	41.2–47.9	56.4 (477)	53.0–59.7
2006	41.4 (357)	38.2–44.7	92.6 (798)	90.7–94.2	45.1 (389)	41.8–48.5	53.2 (459)	49.9–56.6
2007	46.1 (381)	42.7–49.5	89.8 (743)	87.7–91.8	49.8 (412)	46.4–53.2	58.3 (482)	54.9–61.6
2008	47.5 (396)	44.2–50.9	91.7 (764)	89.7–93.4	51.1 (426)	47.8–54.5	58.7 (489)	55.3–62.0
2009	45.3 (413)	42.1–48.5	89.8 (819)	87.7–91.6	50.5 (461)	47.3–53.8	56.5 (515)	53.2–59.7
Sex								
Female	43.5 (624)	41.0–46.1	89.7 (1286)	88.0–91.2	46.4 (665)	43.8–49.0	56.3 (808)	53.8–58.9
Male	44.3 (1659)	42.7–45.9	91.9 (3441)	91.0–92.8	48.3 (1810)	46.8–50.0	56.4 (2112)	54.8–58.0
Age group (years)								
0–39	60.9 (14)	40.6–78.6	78.3 (18)	58.7–91.2	60.9 (14)	40.6–78.6	78.3 (18)	58.7–91.2
40–59	56.8 (353)	52.8–60.6	92.0 (572)	89.6–93.9	60.6 (377)	56.7–64.4	72.0 (448)	68.4–75.5
60–79	48.9 (1588)	47.2–50.6	93.0 (3019)	92.1–93.8	52.7 (1710)	50.9–54.4	61.6 (2001)	59.9–63.3
≥ 80	25.5 (328)	23.2–27.9	86.9 (1118)	85.0–88.7	29.1 (374)	26.7–31.6	35.2 (453)	32.7–37.9
Comorbidity								
Low	48.4 (1384)	46.6–50.3	92.9 (2654)	91.9–93.8	51.7 (1477)	49.9–53.5	60.5 (1728)	58.7–62.2
Medium	40.5 (687)	38.2–42.8	90.6 (1537)	89.1–91.9	44.8 (760)	42.4–47.2	52.7 (895)	50.4–55.1
High	34.0 (212)	30.4–37.8	86.0 (536)	83.2–88.6	38.2 (238)	34.5–42.1	47.7 (297)	43.8–51.6

Abbreviation: CI, confidence interval.

Table 2 Staging of bladder cancer patients in the Danish Cancer Registry

	Localized n (%)	Regional n (%)	Distant n (%)	Unknown n (%)	Total n
Year of diagnosis					
2004	514 (57.2)	42 (4.7)	72 (8.0)	270 (30.1)	898
2005	453 (53.5)	37 (4.4)	88 (10.4)	268 (31.7)	846
2006	455 (52.8)	61 (7.1)	75 (8.7)	271 (31.4)	862
2007	463 (56.0)	43 (5.2)	92 (11.1)	229 (27.7)	827
2008	483 (58.0)	39 (4.7)	82 (9.8)	229 (27.5)	833
2009	536 (58.8)	31 (3.4)	79 (8.7)	266 (29.2)	912
Sex					
Female	687 (47.9)	72 (5.0)	167 (11.6)	508 (35.4)	1434
Male	2217 (59.2)	181 (4.8)	321 (8.6)	1025 (27.4)	3744
Age group (years)					
0–39	10 (43.5)	2 (8.7)	4 (17.4)	7 (30.4)	23
40–59	362 (58.2)	51 (8.2)	88 (14.1)	121 (19.5)	622
60–79	1959 (60.3)	184 (5.7)	310 (9.5)	794 (24.5)	3247
≥80	573 (44.6)	16 (1.2)	86 (6.7)	611 (47.5)	1286
Comorbidity					
Low	1683 (58.9)	174 (6.1)	268 (9.4)	733 (25.6)	2858
Medium	913 (53.8)	66 (3.9)	159 (9.4)	559 (32.9)	1697
High	308 (49.4)	13 (2.1)	61 (9.8)	241 (38.7)	623
Total	2904 (56.1)	253 (4.9)	488 (9.4)	1533 (29.6)	5178

of comorbidity. This resulted mainly from inadequate assessment of lymph node or distant metastases.

In line with our findings, Lau et al found that stage was missing for 63% of all cancers in the American Electronic Medical Records.¹⁴ However, in the US Surveillance, Epidemiology, and End Results (SEER) program, the percentage of unknown stage was only 3% for bladder cancer during the period 2001–2007.¹⁵ In that survey, median age at cancer diagnosis was 78 years, and the distribution of cases between men and women was similar to those in our study. There was no information on the comorbidity level. However, it is unlikely that differences in comorbidity level between Danish patients and patients included in the SEER database could explain the markedly better stage registration among the US patients. Notably, staging in the US survey was performed on the basis of the SEER Summary Stage 2000 (based on pathologic, operative, and clinical information) and not the TNM classification.¹⁶ Registries supplying information to the SEER database are rewarded when performing well in reliability studies. This might be a reason for the higher level of completeness of stage registration in the SEER database than in the DCR.¹⁷ In agreement with our results, several studies on quality of data in cancer registries have found that the percentage of cancer cases with unknown stage increased substantially with increasing age and level of comorbidity.^{18–22} We found

a higher proportion of cancer of unknown stage among women than among men. Also, distant metastases were more frequent among women (Table 2). These are both interesting findings, considering that survival following bladder cancer has been reported to be poorer in women compared with men.²³

We may only speculate on the reasons for the incompleteness in registration of invasive bladder cancer. We found that a large proportion of bladder cancer patients were registered with T1NxMx. A T1 tumor has grown from the layer of cells lining the bladder (mucosa) into the underlying connective tissue (lamina propria), but does not invade the muscle (detrusor) layer of the bladder. T1 tumors invading deeply into the lamina propria have been shown to have a high potential for progressing into T2 tumors, thus affecting the prognosis.^{24,25} However, it is generally clinically accepted that T1 tumors only seldom disseminate. Consequently, most patients with a T1 tumor do not undergo examination for regional or distant metastases. Such cases will be registered with the codes Nx and Mx (as N0 and M0 statuses have not been verified). In that context, a registration of T1NxMx more likely reflects actual clinical practice, rather than incomplete coding. Classification of T1NxMx as a complete registration may thus give a more meaningful estimate on the completeness of stage registration in the DCR.

Bladder cancer is mainly seen in elderly patients.²³ As older age and a higher level of comorbidities are often related, it is conceivable that a substantial proportion of bladder cancer patients are too fragile to endure massive surgery or adjuvant chemotherapy, which is the recommended treatment for advanced or metastatic cancer. The combination of old age and high comorbidity may restrain medical doctors from undertaking further examinations of lymph node and distant metastases status, as complete staging would not affect the treatment choice and would be considered futile from a clinical perspective. Patient choice could have contributed to low TNM completeness, as elderly patients are more likely to refrain from further examinations and exhausting treatment.

In epidemiological research, there are often serious concerns as to how to handle missing data correctly. Our findings indicate that restricting analyses to patients with complete data may yield substantially selected study populations, as missing data are more common among elderly and/or comorbid patients. The presence of lymph node metastasis has been shown to be the most important prognostic factor for bladder cancer mortality.^{26–28} From a clinical point of view, many patients with lymph node metastases will also have distant

“micro-metastases,” and are therefore treated as such. Our results indicate an association between missing data on N stage and high age and/or comorbidity score. This could lead to bias, eg, in prognosis studies. Presence of distant metastasis is also associated with increased mortality and the same arguments thus apply for missing data on M stage.^{29,30} We showed that a clinically based algorithm for tumor stage, allowing for some degree of missing data, could reduce the proportion of tumors of unknown stage markedly. We believe that this algorithm is applicable in both etiologic and prognostic studies of bladder cancer. In such studies, it would be advisable to analyze bladder cancer cases of unknown stage as a separate category. Alternatively, multiple imputation models, predicting values for missing data, may be considered.

Our study design allowed us only to examine the completeness of stage registration based on data in the cancer and hospital registries. In the current setting, we could not examine the accuracy of staging data, and thus evaluate potential errors in data entry, or misclassification. Such information would require medical chart review, or linkage to a valid clinical database, which were beyond the scope of this study. Another limitation of our study derives from the ICD-10 coding practice for bladder cancer in Denmark. Patients presenting with a premalignant bladder tumor will receive an ICD-10 code accordingly. Despite later progression into invasive bladder cancer, no subsequent registration in the DCR will be performed. Hence, by including only incident cancers with ICD-10 code C67, we may miss patients who were initially registered with premalignant bladder tumors.

Stage is often crucial for the choice of treatment of specific cancer types. Therefore, missing data on cancer stage in the DCR may hamper the interpretation of observed differences in treatment and outcome in epidemiologic research. Thus, improvement in the registration of stage for bladder cancer is warranted. However, despite the limitations in the coding of TNM stage for bladder cancer, the DCR is an important resource for epidemiological studies of invasive bladder cancer.

Disclosure

The authors report no conflicts of interest in relation to this work.

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Appendix

Appendix Algorithm for bladder cancer staging according to TNM classification in the Danish Cancer Registry

Stage	TNM codes
Localized	Ta, is, I-4, x N0 M0
	Ta, is, I-2 N0 Mx
	Ta, is, I Nx M0, Mx
Regional	Ta, is, I-4, x N1-3 M0
Distant	Ta, is, I-4, x N1-3 M1
	Ta, is, I-4, x N0 M1
	Ta, is, I-4, x Nx M1
Unknown	T2-4, x Nx M0,x
	T3-4, x N0 Mx
	T1-4, x N1-3 Mx
	T0 N0-3, x M0, I, x

Notes: Ta and Tis apply to noninvasive bladder cancers, however, they are included in the algorithm, due to the possibility of misclassification. T0 denotes cancer of unknown primary localization, only included in the unknown category, again due to possible misclassification. In our material, only four patients were registered with a T0 code.

Abbreviation: TNM, tumor, node, and metastasis.

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