

Completeness of TNM cancer staging for melanoma in the Danish Cancer Registry, 2004–2009

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Background: The purpose of this study was to investigate the completeness of TNM (Tumor, Node, Metastasis) staging of melanoma in the Danish Cancer Registry (DCR).

Methods: We identified 8762 patients with a first primary diagnosis of melanoma from the DCR between 2004 and 2009. We obtained information on level of comorbidity, defined according to the Charlson Comorbidity Index, through the Danish National Patient Register. We computed the completeness of TNM staging overall and by each stage component. Analyses were stratified by gender, age, year of diagnosis, and level of comorbidity. We designed an algorithm that categorized melanoma stage as localized, regional, distant, or unknown. Owing to knowledge on clinical coding practice, we allowed for categorization of tumors with certain missing stage components.

Results: The overall completeness of the TNM staging was 78.4% (95% confidence interval [CI] 77.5–79.3). Completeness varied little by gender and year of diagnosis. However, completeness decreased from 83.5% (95% CI 81.7–85.3) in patients aged 0–39 years to 68.7% (95% CI 65.7–71.6%) in patients 80 years or older, and from 80.3% (95% CI 79.4–81.3) among patients with a low level of comorbidity to 67.4% (95% CI 63.1–71.4) among patients with a high level of comorbidity. Using the algorithm, 87.3% of cases could be assigned to one of the defined stage categories.

Conclusion: The overall completeness of the TNM registration for melanoma was fairly high but varied with age and level of comorbidity. Thus, data on TNM stage should be used with caution in epidemiological and other research.

Keywords: melanoma, neoplasm staging, TNM, Denmark

Introduction

Melanoma is one of the most common types of cancer in Denmark and the incidence has increased markedly during the recent decades, and by more than 50% in the present study period (from 1136 cases in 2004 to 1886 cases in 2009).¹ The prognosis is highly dependent on cancer stage at diagnosis, with 5-year survival decreasing from 95.6% in patients with localized melanoma to 15.7% for melanoma with distant metastasis.^{2,3} Staging of melanoma is performed according to the Tumor Node Metastasis (TNM) classification devised by the American Joint Committee on Cancer, in which a given TNM class reflects the severity and spread of the melanoma at the time of diagnosis.⁴

In Denmark, virtually all patients with incident melanoma have been registered in the Danish Cancer Registry (DCR), along with individual and tumor characteristics.^{5,6} Although the DCR is used extensively for descriptive and analytical epidemiological

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studies, the completeness of the TNM staging has not yet been examined. Knowledge of TNM completeness is important because incomplete stage coding may lead to biased results, especially if the pattern of incompleteness is not random. In this study, we examined the completeness of the TNM staging for melanoma patients in the DCR. To improve our understanding of how the missing data may potentially bias study results, we stratified the analysis of completeness by gender, calendar year, age at diagnosis, and Charlson Comorbidity Index.⁷

Materials and methods

We performed this nationwide study in Denmark, which has a population of approximately 5.4 million inhabitants.⁸ All residents in Denmark are provided with tax-supported medical care. Since 1968, the Danish Civil Registration System has assigned a unique 10-digit personal identification (CPR) number to all Danish residents. This number is used in all Danish registers, allowing unambiguous individual-level data linkage.^{9,10}

Ascertainment of patients with melanoma

From the DCR, we identified all patients with a primary diagnosis of melanoma (International Classification of Disease, 10th revision [ICD-10] C43) between January 1, 2004 and December 31, 2009. The DCR has recorded information on incident cancers in the Danish population since 1943.^{5,6} Cancer diagnoses have been registered according to the ICD-10 since 1978. Since 2004, stage has been recorded using the TNM classification.^{6,11,12} From the DCR, we obtained information on date of diagnosis, age, gender, and TNM codes.

Comorbidity data

Data on the presence of comorbidity were obtained from the Danish National Patient Register (DNPR).¹³ The DNPR contains data on all admissions to nonpsychiatric hospitals in Denmark since 1977 and outpatient contacts since 1995 including the CPR number, date of admission/contact and discharge, and diagnosis codes. We described pre-existing comorbidity using the Charlson Comorbidity Index (CCI) based on hospital diagnoses within 10 years preceding the date of melanoma diagnosis.^{7,14} We categorized CCI scores into 0 (low), 1–2 (medium), and 3+ (high). Thygesen et al has recently reported that positive predictive values of CCI diagnoses in the DNPR are high (98.0%, 95% confidence interval [CI] 96.9–98.8).¹⁴

Statistical analysis

We computed the completeness and corresponding 95% CI of the TNM staging overall and by each component individually (ie, T, N, and M). Registration of Tx, Nx, and Mx (denoting that information on tumor size, lymph node metastasis, and distant metastasis were not available or could not be assessed) was defined as incomplete. Completeness was calculated as the number of individuals with a complete TNM recording, divided by the total number of patients. We stratified completeness by gender, age (0–39 years, 40–59 years, 60–79 years, and ≥80 years), year of cancer diagnosis, and level of comorbidity. Melanomas with a thickness of 1 mm or thinner (T1) are typically localized and considered non-metastatic, hence patients with these lesions are often not offered sentinel node operation and further examination. Therefore, Nx and Mx are often used for T1 melanomas because N0 and M0 status has not been confirmed. Therefore, as a sensitivity analysis, we conducted a subanalysis in which we included melanomas assigned T1, Nx, Mx in our definition of complete staging. In addition, we performed a sensitivity analysis restricted to patients with histologically verified melanoma. Finally, we designed an algorithm that allowed us to categorize stage as localized, regional, distant, or unknown according to the codes for “T” (tumor), “N” (lymph node), and “M” (metastasis), as shown in Appendix 1. For each of the three definite stages, missing data were allowed if the available information provided sufficient and clinically meaningful information to categorize cases. The unknown tumor category included primarily locally advanced tumors (T3 or T4) with unknown N and/or M stage.

Analyses were performed using SAS (version 9.2; SAS Institute Inc, Cary, NC).

Results

We identified 8762 patients registered with primary melanoma in the DCR from 2004 to 2009. Of these, 4844 (55.3%) were women, and the median age at diagnosis was 56 years (interquartile range 41–69 years) for women and 62 years (interquartile range 50–72 years) for men.

The overall completeness of the TNM staging was 78.4% (95% CI 77.5–79.3, Table 1) and the proportion increased only marginally by redefining T1, Nx, Mx as complete (80.0% [95% CI 79.2–80.8]). Nearly all melanoma cases were histologically verified (96.8%), and thus restricting the analyses to these did not change the overall completeness (78.5% versus 78.4%). During the study period, TNM completeness was slightly higher for women than for men, 80.1% (95% CI 79.0–81.2) versus 76.3% (95% CI 74.9–77.6), but otherwise

Table 1 Completeness of TNM staging among melanoma patients in the Danish Cancer Registry

	Total number of patients	TNM completeness		T completeness		N completeness		M completeness	
		n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Total	8762	6869	78.4 (77.5–79.3)	7754	88.5 (87.8–89.2)	7424	84.7 (84.0–85.5)	7770	88.7 (88.0–89.3)
Gender									
Female	4844	3880	80.1 (79.0–81.2)	4345	89.7 (88.8–90.5)	4153	85.7 (84.7–86.7)	4326	89.3 (88.4–90.2)
Male	3918	2989	76.3 (74.9–77.6)	3409	87.0 (85.9–88.0)	3271	83.5 (82.3–84.6)	3444	87.9 (86.9–88.9)
Age group (years)									
0–39	1615	1349	83.5 (81.7–85.3)	1497	92.7 (91.4–93.9)	1417	87.7 (86.1–89.3)	1474	91.3 (89.8–92.6)
40–59	2845	2299	80.8 (79.3–82.2)	2546	89.5 (88.3–90.6)	2459	86.4 (85.1–87.7)	2569	90.3 (89.2–91.4)
60–79	3334	2556	76.7 (75.2–78.1)	2899	87.0 (85.8–88.1)	2805	84.1 (82.9–85.3)	2935	88.0 (86.9–89.1)
≥80	968	665	68.7 (65.7–71.6)	812	83.9 (81.5–86.1)	743	76.8 (74.0–79.3)	792	81.8 (79.3–84.2)
Year of diagnosis									
2004	1152	867	75.3 (72.7–77.7)	958	83.2 (80.9–85.2)	978	84.9 (82.7–86.9)	1005	87.2 (85.2–89.1)
2005	1400	1115	79.6 (77.5–81.7)	1228	87.7 (85.9–89.4)	1221	87.2 (85.4–88.9)	1265	90.4 (88.7–91.8)
2006	1430	1152	80.6 (78.5–82.6)	1311	91.7 (90.2–93.0)	1244	87.0 (85.2–88.7)	1301	91.0 (89.4–92.4)
2007	1481	1156	78.1 (75.9–80.1)	1314	88.7 (87.0–90.3)	1220	82.4 (80.4–84.3)	1302	87.9 (86.2–89.5)
2008	1478	1125	76.1 (73.9–78.2)	1315	89.0 (87.3–90.5)	1227	83.0 (81.0–84.9)	1273	86.1 (84.3–87.8)
2009	1821	1454	79.8 (78.0–81.6)	1628	89.4 (87.9–90.8)	1534	84.2 (82.5–85.9)	1624	89.2 (87.7–90.6)
CCI score									
Low (0)	6722	5401	80.3 (79.4–81.3)	6031	89.7 (89.0–90.4)	5801	86.3 (85.5–87.1)	6029	89.7 (89.0–90.4)
Medium (1–2)	1559	1144	73.4 (71.1–75.5)	1328	85.2 (83.4–86.9)	1260	80.8 (78.8–82.7)	1334	85.6 (83.8–87.3)
High (3+)	481	324	67.4 (63.1–71.4)	395	82.1 (78.5–85.4)	363	75.5 (71.5–79.2)	407	84.6 (81.2–87.6)
Subanalysis	8762	7011	80.0 (79.2–80.8)						

Abbreviations: CI, confidence interval; CCI, Charlson Comorbidity Index (excluding melanoma); TNM, tumor, node, metastasis.

did not reveal any overall trends. In contrast, completeness declined with increasing age, from 83.5% (95% CI 81.7–85.3) among patients aged 0–39 years to 68.7% (95% CI 65.7–71.6) in those aged 80 years or more, as well as with level of comorbidity, from 80.3% (95% CI 79.4–81.3) in patients with low comorbidity (CCI score 0) to 67.4% (95% CI 63.1–71.4) among those with high level of comorbidity (CCI score 3+). When examining the completeness of T, N, and M separately, we observed a slightly lower completeness of N (84.7%) compared with T (88.5%) and M (88.7%). Similar to the overall TNM registration, the completeness of the individual stage components decreased with increasing age and level of comorbidity.

Using the algorithm (Appendix 1), allowing Tx, Nx, and Mx codes to be included in the definite stage categories, the proportion of tumors with unknown stage decreased from 21.6% to 12.7% (Table 2). Compared with patients with known cancer stage, patients with unknown cancer stage were more frequently males (49.8% versus 44.0%) and of higher age (80 years or more, 18.2% versus 10.0%). Furthermore, medium or high CCI scores were assigned to 30.0% of those with unknown cancer stage compared with 22.3% of those with known cancer stage. The staging completeness among patients aged 0–39 years was 90.5%, and 79.0% among those aged 80 years or more. Among patients with low comorbidity,

the completeness was 88.4% versus 82.1% among those with high level of comorbidity.

Discussion

In this nationwide study, we found an overall completeness of TNM staging for melanoma of 78%. The completeness varied by age and level of comorbidity and was lowest among the elderly and those with high levels of comorbidity. When we applied a stage algorithm that allowed some missing values of T, N, and M, the overall proportion of patients with unknown stage decreased to 12.7%; however, elderly and/or high comorbidity patients still exhibited the highest proportions of unknown stage. To our knowledge, no studies have yet evaluated the completeness of the TNM staging in the DCR. Compatible with our findings, studies of other cancer registries have shown that the proportion of patients with unknown cancer stage is higher for elderly patients with breast, prostate, and colorectal cancer.^{15,16}

Based on our results and those of other studies, it is imperative to consider the variation in TNM staging according to age and level of comorbidity in studies based on cancer registry data. Restricting analyses to patients with complete data on staging is likely to introduce selection bias and lead to incorrect conclusions. In some studies, cases of unknown stage have been categorized as a separate group, or they have been combined

Table 2 Staging of melanoma patients in the Danish Cancer Registry by year of diagnosis, gender, age group, and CCI score

	Cancer stage									
	Localized		Regional		Distant		Unknown stage		Known stage	
	n	%	n	%	n	%	n	%	n	%
Total	6621	75.6	660	7.5	367	4.2	1114	12.7	7648	87.3
Gender										
Female	3825	79.0	305	6.3	155	3.2	559	11.5	4285	88.5
Male	2796	71.4	355	9.1	212	5.4	555	14.2	3363	85.8
Age group (years)										
0–39	1327	82.2	102	6.3	33	2.0	153	9.5	1462	90.5
40–59	2179	76.6	240	8.4	121	4.3	305	10.7	2540	89.3
60–79	2434	73.0	278	8.3	169	5.1	453	13.6	2881	86.4
≥80	681	70.4	40	4.1	44	4.5	203	21.0	765	79.0
Year of diagnosis										
2004	808	70.1	108	9.4	53	4.6	183	15.9	969	84.1
2005	1066	76.1	112	8.0	63	4.5	159	11.4	1241	88.6
2006	1126	78.7	106	7.4	58	4.1	140	9.8	1290	90.2
2007	1106	74.7	111	7.5	58	3.9	206	13.9	1275	86.1
2008	1118	75.6	107	7.2	66	4.5	187	12.7	1291	87.3
2009	1397	76.7	116	6.4	69	3.8	239	13.1	1582	86.9
CCI score										
Low (0)	5204	77.4	522	7.8	216	3.2	780	11.6	5942	88.4
Medium (1–2)	1114	71.5	111	7.1	86	5.5	248	15.9	1311	84.1
High (3+)	303	63.0	27	5.6	65	13.5	86	17.9	395	82.1

Abbreviation: CCI, Charlson Comorbidity Index (excluding melanoma).

with the definite stage category (eg, distant) that they resemble the most in terms of survival or other characteristics. However, studies have revealed that patients with unknown cancer stage do not typically resemble patients with metastases.^{2,17} In a study of survival of melanoma patients in the United States during the period 1992 to 2005, Pollack et al reported that patients with unknown cancer stage had a 5-year survival of 80.3% compared with 95.6% for patients with localized melanoma and 63.7% for those with regional disease.² Alternatively, patients with missing data on stage can be replaced by plausible values predicted from individuals with available data using statistical methods such as multiple imputation.^{16,18}

The main strengths of our study include the nationwide approach using data from a cancer registry with virtually complete registration of melanoma and other cancer diagnoses, its large size, and the availability of data from civil and patient registers that enabled us to examine TNM completeness according to level of comorbidity. However, we only examined the completeness of the TNM staging, and our study approach did not allow for any evaluation of the accuracy of the TNM coding.

Conclusion

In conclusion, we found that the overall registration of TNM staging for melanoma in the DCR was fairly high. However, older age and a higher level of comorbidity were associated

with incomplete TNM registration. Thus, data on TNM stage should be used with caution in epidemiological and other research, with consideration of missing data according to age and level of comorbidity.

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Disclosure

The authors report no conflicts of interest in this work.

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Appendix table

Appendix I Algorithm for staging of melanoma according to the TNM classification

Stage	TNM classification
Localized	T1 Nx M0, x T1–2 N0 Mx T1–4, x N0 M0
Regional	T1–4, x N1–3 M0
Distant	T1–4, x N0–3, x M1
Unknown	T1–4, x N1–3 Mx T2–4, x Nx M0, x T3–4, x N0 Mx

Note: 24 patients (0.3%) coded with T0, Ta, or Tis were added to the unknown stage category, since these codes are not clinically meaningful for melanoma.

Abbreviation: TNM, tumor, node, metastasis.

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