

ORIGINAL ARTICLE



Influence of various assumptions for the individual TNM components on the TNM stage using Nordic cancer registry data

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ABSTRACT

Background: The stage at diagnosis is one of the most important predictors for cancer survival. TNM stage is constructed from T (tumor size), N (nodal spread), and M (distant metastasis) components. In many notifications to cancer registries, TNM information is incomplete with unknown N and/or M. We aimed to evaluate the influence of various assumptions for recoding missing N (NX) and M (MX) as N0 and M0 on the proportion with available TNM stage, stage-distribution, and stage-specific relative survival.

Material and Methods: We identified 140,201 patients diagnosed with incident cancer of the colon, rectum, lung, breast, or kidney during 2014–2016 in Denmark, Norway, Sweden, or Iceland. Information on TNM were obtained from cancer registry records used for an update of the Nordic cancer statistics database NORDCAN. Patients were followed for death or emigration through 2017. We calculated proportions of available TNM stage, stage distribution, and stage-specific relative survival under different approaches for each cancer site and country.

Results: Application of the assumptions yielded higher numbers of cases with available TNM stage for stages 0–I, II, and III. We observed only minor differences in stage-specific one-year relative survival when applying N0M0 for missing N and M, especially for high completeness of TNM registrations, whereas relative survival for remaining cases with missing TNM stage declined substantially.

Conclusion: We found no major changes in stage-specific one-year relative survival applying N0M0 for NXMX. We conclude that complete TNM information is preferable to making assumptions, but it seems reasonable to consider assuming N0M0 for missing N and M in future studies based on the Nordic cancer registries. An automatic algorithm, though, is not recommended without considering potential area-specific reasons for frequent use of NX and MX. Clinicians should be urged to report complete TNM information to improve surveillance of the TNM stage.

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Background

Cancer staging using tumor size (T), nodal spread (N) and distant metastasis (M), known as the TNM stage classification, is an important tool in the management of cancer patients and one of the most important predictors for cancer survival [1,2]. Moreover, information on TNM-staging is a valuable tool in empirical research, e.g., epidemiological cancer surveillance studies based on cancer registry data [1]. The TNM stage is cancer site-specific and derived from three components: T (main values 1–4), describing the extent of the primary tumor, N (0–3) denoting the absence or presence and extent of regional lymph node metastases, and M (0,1) denoting absence or presence of distant metastases. The TNM stage can be assessed and registered as a clinical classification, cTNM, or a postsurgical histopathological classification, pTNM. Manuals for TNM-staging are updated regularly

and provide specifics at the cancer site-specific level on how each component, i.e., T, N, and M, should be assessed and the final TNM stage determined [1].

Knowledge of all three TNM components are necessary to determine the TNM stage except when M1 is registered. In that case, the TNM stage is always stage IV. However, many cancer notifications to cancer registries report values of T but with unknown N and M (NXMX), or with unknown M (MX), thus hindering the determination of the TNM stage according to guidelines. Clinicians may report MX for cases in which the clinical work-up has not established with confidence that cancer is not disseminated. To determine a TNM stage for such a case, various assumptions can be applied, e.g., by assuming that if the T and N components are available, MX can be interpreted as M0. Such assumptions are often applied in international studies comparing country-specific stage-distribution and relative survival for a cancer site,

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e.g., the SurvMark2 project; however, the specific influence of these assumptions has not been validated [3–5]. In fact, the use of MX is not in accordance with the TNM manual 7th edition [6] stating ‘If there is doubt concerning the correct T, N or M category to which a particular case should be allotted, then the lower (i.e., less advanced) category should be chosen. This should also be reflected in the stage grouping’. Moreover, the manual reads for cTNM ‘The MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone (the use of MX may result in exclusion from staging)’, and for pTNM ‘pM0 and pMX are not valid categories’.

In the present study, we aimed to evaluate the influence of various assumptions for recoding missing N (NX) and M (MX) as N0 and M0 on the proportion of patients with available TNM stage and stage-distribution for five major cancer sites (colon, rectum, lung, breast, and kidney) in the Nordic cancer registries. We also estimated the impact of different assumptions on one-year relative survival.

Material and methods

From the nationwide cancer registries of Denmark, Norway, Sweden, and Iceland [7], we identified all cancer patients diagnosed with incident cancer of the colon, rectum, lung, breast, or kidney during 2014–2016. Patients were followed for death or emigration until the end of 2017. Key cancer data, including TNM information, were obtained from the cancer registries. Specifically, the data were derived from national deliveries to the NORDCAN secretariat in Denmark for the annual update of the NORDCAN cancer statistics database for inclusion of 2016 cancer data. For Iceland, no TNM data were available for lung and kidney cancer. In the cancer registries of Norway and Iceland, both clinical (cTNM) and pathological (pTNM) stage could be reported for a cancer case, whereas the clinical or pathological basis for the TNM registration were not specified in Denmark and Sweden. In Norway, cTNM was derived from notifications to the cancer registry from clinicians and pTNM information from the clinical/quality registers [8]. For kidney cancer in Norway, only cTNM was available. In Iceland, cancer registry staff collected information on TNM from the hospital medical records. We chose to use the maximum values of T, N, and M corresponding to the practice in the Danish Cancer Registry [7]. In Denmark and Sweden, reporting of TNM to the cancer registries for incident cancers has been mandatory since 2004. For Denmark, TNM registrations come from the inpatient hospital register. In Sweden, most of the TNM registrations in the Cancer Registry are transferred from clinical quality registers [8].

Using the 7th edition of the TNM manual [6], we transformed T, N, and M to the TNM stage for each case according to TNM guidelines for the specific cancer site. We used NORDCAN entities for the identification of the five chosen cancer sites, i.e., colon ICD10: C18, rectum C19–20, lung C33–34, breast C50, and kidney C64. Appendix (C18.1) was transformed as a separate TNM-site, while no transformation was

feasible for the trachea (C33) and, thus, only M1 could be registered.

From valid values of the T, N, and M components, we categorized the TNM stage as 0, I, II, III, and IV. For simplification, we combined TNM stages 0–I. In a clinical context, this would not be sufficiently detailed, but the combination is appropriate for surveillance purposes. We applied various assumptions for missing values of N and M and established three approaches for assessing the TNM stage: (A1) ‘Strict’ TNM-rules requiring that all three components (T, N, and M) were available except if M1 was noted. When both cTNM and pTNM were available, we used the highest T, N, and M values; (A2) based on A1 values, M0 was used for MX if valid T and N were available; and (A3) on top of A2, N0 was used for NX if a valid T was present. Moreover, we defined two categories for cases with missing TNM stage: ‘No info’ included cases with no information, i.e., TXNXMX, independent of the assumptions. ‘Partly info’ included cases with MX and valid T and/or N value, and cases with M0 but a non-valid T and/or N. These cases were included according to the three assumptions (A1–A3).

As a sensitivity analysis for Norway and Iceland, we also compared approach A3 to an alternative approach commonly used in international comparisons, i.e., preferring pTN above cTN and cM above pM, unless pM1 was registered (A3-path).

Statistical methods

We calculated the number of cases and the proportions with the available TNM stage for the three approaches. Secondly, we calculated the difference in percentage points (pp) in a stepwise comparison to the preceding approach for the five sites for the four countries. Finally, we estimated the number of additional/relocated cases proceeding from approach A1 through A3 and their distribution by TNM stage categories.

For each cancer site and country, and for approach A1 and A3 specifically, we assessed the distribution by the various missing categories and available TNM stage, as well as the stage distribution among those with available TNM stage. This was supplemented with an assessment of the difference in pp between approach A1 and A3.

For each cancer site, we estimated one-year age-standardised relative survival for all cases diagnosed in the study period (2014–2016; followed through 2017), and separately for the missing group and stage-specific groups. We used the Pohar-Perme method [9] with relative age weights [10] according to an adapted version of the International Cancer Survival Standard 1 (ICSS1; see [Supplementary Table 1](#)). We used the `strs` command in Stata to calculate relative survival and confidence intervals (CI), with the `indweight` option for individual weights [11]. For approach A3, we computed one-year relative survival estimates with 95% confidence intervals, as well as the difference to the point estimate of survival for A1, for the five cancer sites and four countries. In the survival calculations cases diagnosed *via* death certificates alone (DCO) or incidental findings at autopsy were excluded, while the cases are included in the ‘No info’ category in tabulations

of stage distributions. The proportions were rather low, below 1% for most, but highest for kidney and lung cancer, in Norway respectively 3.3 and 2.9%.

Results

We identified a total of 140,201 patients for the five cancer sites in the four Nordic countries (Table 1). Across cancer site and country, the number of cases with available TNM stage information increased from the strict approach (A1), over the assumption of using M0 for MX (A2), to the assumption of N0M0 for records of NXMX (A3). For colon, rectum, and lung cancer, Norway displayed lower proportions of cases with available TNM stage under the strict approach (A1) than the other countries. Norway had less than 50% cases with available TNM stage for colon and rectum and 67% for lung cancer, and we observed the largest increases in proportions proceeding from approach A1 to A2 for the three cancers (+40.9 pp, +27.5 pp, and +9.6 pp, respectively). In Denmark, substantial increases in the proportion of cases with available TNM stage were observed proceeding from A2 to A3 and applying N0 for NX on top of the A2 assumption (M0 for MX) in records of the colon (+5.1 pp), rectum (+9.9 pp) and kidney cancer (+9.4 pp).

Assuming N0 and M0 for missing N and M increased the availability of TNM stage to more than 75% in Norway (except for kidney cancer) and to 80%, 90%, and 90% or more, respectively, in Denmark, Iceland, and Sweden (Table 1).

For breast cancer, the proportion of cases with available TNM stage increased the most (+12.1 pp) in Iceland when applying the criteria for approach A3, but all four countries exhibited a high proportion (89% or more) of cases with available TNM stage under A3. For kidney cancer, the

available proportions increased with +11.4 pp to 89% in Denmark and with +7.6 pp to 96% in Sweden, while Norway displayed an increase of +6.8 pp, although with less than 50% cases with available TNM under A3. For all five cancer sites, Sweden had nearly 85% cases with available TNM stage under A1 and 90% or more under A3.

The numbers of relocated cases with now available TNM stage proceeding from approach A1 to A3 were highest for Norway for colon, rectum, and lung cancer, while for breast and kidney cancer, we observed the highest numbers for Denmark. These cases were relocated to TNM stages 0–I, II, and III and for kidney cancer supplemented with a few cases relocated to TNM stage IV. The distributions of the TNM stage categories varied between countries, but only with minor variations for kidney cancer.

Table 2 shows the distribution of cases by type of missing or available TNM stage, and the distribution by TNM stage categories for those with available TNM stage, for both the strict approach (A1) and under the assumption of N0M0 for NXMX (A3). The proportion of cases with no TNM information ('No info') differed between countries and was highest for Norway, except for breast cancer in Denmark. The proportion of cases with partial information ('Partly info') decreased substantially proceeding from A1 to A3. Under A3, the remaining cases were mainly those with invalid or missing T and was lower than 3% in the five countries, except for colon and rectum cancer in Denmark and rectum in Iceland exhibiting proportions of 5–7%. Norway displayed the largest gains in cases with available TNM stage proceeding from approach A1 to A3 for colon, rectum, and lung cancer. Under approach 3, the proportions of cases in stage IV were lower in Norway than in the other countries, except for breast cancer.

Supplementary Table 2 shows the availability of cTNM

Table 1. Number of cases, available TNM stage information under three approaches (A1, A2, A3) and increase from previous approach, and percentage distribution by TNM stage of the relocated cases from A1 to A3 by cancer site and country for the period 2014–2016.

	Cases	Available percentage TNM-stage			Relocated cases and their TNM-stage %				
		A1	A2 (dif A2-A1)	A3(dif A3-A2)	Number	0–I	II	III	IV
Colon									
Denmark	11032	69.6	75.4 (5.8)	80.5 (5.1)	1203	35	42	24	0
Norway	8778	41.7	82.6 (40.9)	85.1 (2.5)	3810	22	41	37	0
Sweden	12719	89.3	89.9 (0.4)	92.9 (3.0)	467	64	26	10	0
Iceland	378	80.7	86.2 (5.5)	89.4 (3.2)	33	58	15	27	0
Rectum									
Denmark	5156	65.3	69.5 (4.2)	79.4 (9.9)	724	40	41	19	0
Norway	4066	43.7	71.2 (27.5)	75.1 (3.9)	1277	34	34	32	0
Sweden	6228	84.7	85.5 (0.8)	90.0 (4.5)	332	78	15	6	0
Iceland	147	78.9	82.3 (3.4)	88.4 (6.1)	14	64	14	21	0
Lung									
Denmark	14106	93.5	95.1 (1.6)	95.7 (0.6)	319	22	17	61	0
Norway	9199	67.4	77.0 (9.6)	78.0 (1.0)	974	47	20	34	0
Sweden	12088	95.9	96.1 (0.2)	96.4 (0.3)	64	41	34	25	0
Breast									
Denmark	14292	78.8	84.0 (5.2)	89.0 (5.0)	1457	32	46	22	0
Norway	10174	94.6	96.3 (1.7)	97.6 (1.3)	299	4	85	11	0
Sweden	22058	95.3	95.4 (0.1)	96.0 (0.6)	164	38	51	11	0
Iceland	648	83.0	83.8 (0.8)	95.1(11.3)	78	54	38	8	0
Kidney									
Denmark	2845	77.4	79.4 (2.0)	88.8 (9.4)	325	62	15	20	2
Norway	2574	42.5	43.8 (1.3)	49.3 (5.5)	174	64	14	20	2
Sweden	3713	88.8	89.2 (0.4)	96.4 (7.2)	280	69	12	18	1

A1: Maximum T, N and M from cTNM and pTNM and valid T, N and M; A2: Assuming M0 for MX; A3: Assuming N0M0 for NXMX.

Table 2. TNM-stage information in percent in approach A1 and A3 and percentage point change for years 2014–2016 by cancer site and four Nordic countries.

	Denmark			Norway			Sweden			Iceland		
	A1	A3	Δpp	A1	A3	Δpp	A1	A3	Δpp	A1	A3	Δpp
Colon												
No info	12.3	12.3		13.5	13.5		5.7	5.7		7.1	7.1	
Partly	18.1	7.2		44.8	1.4		5.0	1.4		12.2	3.4	
TNM-inf	69.6	80.5	10.9	41.7	85.1	43.4	89.3	92.9	3.6	80.7	89.4	8.7
0–I	19.1	21.2	2.1	11.8	17.0	5.2	15.0	17.0	2.0	16.1	20.1	4.0
II	29.6	31.2	1.6	28.1	34.7	6.6	31.9	31.6	–0.3	25.9	24.9	–1.0
III	25.6	25.4	–0.2	26.6	31.9	5.3	31.8	31.0	–0.8	26.2	26.3	0.1
IV	25.7	22.2	–3.5	33.5	16.4	–17.1	21.3	20.4	–0.9	31.8	28.7	–3.1
Rectum												
No info	14.0	14.0		23.4	23.4		8.2	8.2		6.1	6.1	
Partly	20.7	6.6		32.9	1.5		7.1	1.8		15.0	5.4	
TNM-inf	65.3	79.4	14.1	43.7	75.1	31.4	84.7	90.0	5.3	78.9	88.4	9.5
0–I	25.0	27.7	2.7	18.8	25.1	6.3	26.9	29.9	3.0	15.5	20.8	5.3
II	21.7	25.1	3.4	23.5	27.9	4.4	22.1	21.7	–0.4	16.4	16.2	–0.2
III	31.5	29.2	–2.3	32.3	32.2	–0.1	31.4	29.9	–1.5	50.9	47.7	–3.2
IV	21.9	18.0	–3.9	25.4	14.8	–10.6	19.6	18.5	–1.1	17.2	15.4	–1.8
Lung												
No info	3.3	3.3		18.8	18.8		3.4	3.4				
Partly	3.2	1.0		13.8	3.2		0.7	0.2				
TNM-inf	93.5	95.7	2.2	67.5	78.0	10.5	95.9	96.4	0.5			
0–I	17.5	17.6	0.1	19.7	23.3	3.6	19.2	19.3	0.1			
II	8.8	9.0	0.2	8.4	10.0	1.6	7.2	7.4	0.2			
III	21.7	22.6	0.9	17.7	19.8	2.1	19.9	20.0	0.1			
IV	52.0	50.8	–1.2	54.2	46.9	–7.3	53.6	53.3	–0.3			
Breast												
No info	9.3	9.3		2.4	2.4		3.6	3.6		3.9	3.9	
Partly	11.9	1.7		3.0	0		1.1	0.4		13.1	1.1	
TNM-inf	78.8	89.0	10.2	94.6	97.6	3.0	95.3	96.0	0.7	83.0	95.1	12.1
0–I	51.8	49.5	–2.3	40.4	39.3	–1.1	55.4	55.3	–0.1	35.3	37.7	2.4
II	37.4	38.3	0.9	42.8	44.0	1.2	37.5	37.6	0.1	41.1	40.7	–0.4
III	7.0	8.8	1.8	13.1	13.0	–0.1	4.2	4.3	0.1	16.5	15.4	–1.1
IV	3.8	3.3	–0.5	3.8	3.7	–0.1	2.8	2.8	0.0	7.1	6.2	–0.9
Kidney												
No info	10.2	10.2		50.2	50.2		2.8	2.8				
Partly	12.4	1.0		7.3	0.5		8.4	0.8				
TNM-inf	77.4	88.8	11.4	42.5	49.3	6.8	88.8	96.4	7.6			
0–I	52.0	53.3	1.3	65.7	65.5	–0.2	55.5	56.5	1.0			
II	8.1	9.0	0.9	10.9	11.3	0.4	9.9	10.1	0.2			
III	16.8	17.3	0.5	10.6	11.8	1.2	16.0	16.2	0.2			
IV	23.1	20.4	–2.7	12.9	11.3	–1.6	18.6	17.2	–1.4			

No info: No TNM information; Partly: Incomplete TNM information; Δpp: change in percentage point in available TNM stage information from approach A1 to A3; A1: Maximum T, N and M from cTNM and pTNM and valid T, N and M; A3: Assuming N0M0 for NXMX. Proportions of TNM stages 0–I, II, III and IV sum to 100%, discrepancies are due to rounding.

and pTNM in Norway and Iceland. For most colon cancer cases, pTNM was registered, and 33% of Norwegian cases and 10% of the Icelandic had records of both pTNM and cTNM. For rectum cancer, information on pTNM was also frequent and 27% in Norway and 56% in Iceland had both pTNM and cTNM. In Norway, 34% of lung cancer cases had both records with cTNM as the more frequent. Both records were available for 79% of breast cancer cases in Norway, while for breast cancer in Iceland, cTNM was the most common and only 8% of cases had records of both.

In a sensitivity analysis, we compared TNM stage distributions between approach A3-path (preference of pTNM above cTNM) and the primary approach A3 (maximum of T, N, and M from cTNM and pTNM) for Norway and Iceland (Supplementary Table 3). Our approach (A3) exhibited higher TNM stages than the sensitivity approach (A3-path). The largest differences in stage distribution were seen for rectum cancer in Iceland and breast cancer in Norway.

Table 3 shows age-standardised one-year relative survival estimates with 95% CI by country and cancer site for (i) all cases, (ii) for the group of cases with missing TNM stage, and (iii) according to TNM stage under approach A3 (assuming N0M0 for NXMX). Generally, survival decreased with higher stage while survival estimates for 'Missing' fell in the range between the survival estimates for stage III and IV. For each TNM stage level, the survival estimates were similar between countries, although slightly lower in Iceland for colon and rectal cancer and in Sweden for colon, rectum, and breast cancer, especially for stage IV.

Table 3 also displays changes in survival percentages for approach A3 compared with those under the strict TNM-rules (A1) for each stage level (missing, 0–I, II, III, IV). Figure 1 shows the survival estimates with 95%CI for both approach A1 and A3 for colon cancer. We observed the largest changes in survival for the 'Missing' category. Under A3, survival estimates for the missing category were closer to stage IV survival than under A1. Overall, proceeding from A1 to A3, the stage-specific survival decreased slightly for stages 0–I, II, and III, with the largest decrease occurring for stage III. The largest differences were seen for stage III colon and lung cancer in Norway and for stage III breast cancer and stage II rectum cancer in Denmark.

Discussion

For the five selected cancer sites (colon, rectum, lung, breast, and kidney) in patients diagnosed 2014–2016 in Denmark, Norway, Sweden, and Iceland, we found only minor decreases in TNM stage-specific one-year relative survival when assuming N0M0 for NXMX in cases with known T. After the relocation of most cases with partly TNM information by implementing assumptions, the remaining group with missing TNM stage had substantially decreased survival. This might indicate that many of the relocated cases would have been registered with N0M0 if clinicians had reported complete TNM and that the remaining cases with missing TNM stage (mostly cases with no TNM information at all) would hold a majority of cases with distant spread and no treatment.

The Swedish data exhibited the smallest change in TNM stage availability due to the high proportion of cases with complete records of TNM, whereas we observed larger differences in the availability of TNM in Norway after applying the assumptions (A3) due to the initial low proportion of complete reports. The between-country variation in distributions of TNM stages for the relocated cases likely indicates that the reasons for incomplete and missing TNM registration differ between countries.

Before applying the assumption of M0N0 for MXNX for a specific cancer site, additional information on the country-specific use of MX and NX should be retrieved, and tabulations as presented herein could further qualify the decision on which assumptions to apply. For instance, in Denmark, the proportion of cases with known TNM stage for lung cancer increased from 85% to 96% when applying the A3 approach. The clinical database for lung cancer in Denmark,

Table 3. One-year relative survival (95%CI) by TNM stage under assumption A3 and percentage point change (Δ pp) in survival between A3 and A1 for the five selected cancer sites diagnosed 2014–2016 in four Nordic countries.

Colon	Denmark		Norway		Sweden		Iceland	
	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp
All	86.1 (85.3–86.8)	.	85.3 (84.4–86.1)	.	84.2 (83.5–84.9)	.	80.4 (75.9–84.2)	.
Missing	83.2 (81.4–84.9)	–2.7	61.3 (58.2–64.3)	–24.6	51.6 (47.8–55.3)	–13.6	55.0 (27.4–75.9)	–22.1
0–I	97.7 (96.3–98.6)	–0.7	99.0 (97.4–99.6)	–0.4	98.9 (97.9–99.4)	–0.2	99.7 (0.0–100.0)	0.2
II	96.3 (95.4–97.1)	–1.3	96.7 (95.8–97.5)	–0.6	96.8 (96.0–97.4)	–0.7	96.7 (89.3–99.0)	–0.4
III	92.1 (90.8–93.2)	–1.0	90.6 (89.3–91.9)	–5.0	91.6 (90.5–92.5)	–0.2	90.4 (80.7–95.4)	–0.8
IV	57.8 (55.5–60.0)	0.0	59.8 (56.9–62.5)	0.0	54.8 (52.7–56.9)	0.0	52.3 (41.5–62.0)	0.0
Rectum	Denmark		Norway		Sweden		Iceland	
	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp
All	89.2 (88.2–90.1)	.	89.7 (88.6–90.7)	.	87.7 (86.8–88.6)	.	83.1 (75.0–88.8)	.
Missing	86.4 (84.0–88.5)	–2.3	78.8 (76.0–81.3)	–10.3	66.8 (62.4–70.8)	–10.1	63.0 (12.8–90.1)	–6.1
0–I	96.8 (95.0–98.0)	–0.6	99.9 (0.0–100.0)	–0.3	98.8 (97.6–99.4)	0.3	94.8 (64.0–99.4)	–8.8
II	94.4 (92.5–95.8)	–2.6	96.5 (94.6–97.8)	0.6	96.7 (95.2–97.7)	–0.8	96.1 (79.8–99.3)	1.4
III	95.1 (93.4–96.4)	–0.2	95.2 (93.3–96.5)	–1.0	93.0 (91.5–94.3)	–0.2	88.8 (74.0–95.4)	–2.9
IV	65.5 (61.8–69.0)	0.0	70.6 (65.8–74.8)	0.0	62.4 (59.3–65.4)	0.0	53.6 (26.3–74.7)	0.0
Lung	Denmark		Norway		Sweden		Iceland	
	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp
All	50.7 (49.8–51.7)	.	50.6 (49.4–51.8)	.	52.6 (51.6–53.6)	.	.	.
Missing	45.3 (40.0–50.4)	2.3	38.5 (35.9–41.1)	–14.1	42.7 (36.3–48.9)	–3.6	.	.
0–I	91.1 (89.8–92.3)	–0.5	92.5 (90.8–93.9)	0.8	94.2 (93.0–95.2)	–0.2	.	.
II	81.0 (78.7–83.1)	–1.6	84.1 (81.2–86.5)	–1.1	80.5 (77.3–83.2)	–0.7	.	.
III	60.3 (58.3–62.2)	–2.1	60.3 (57.4–63.1)	–3.1	60.7 (58.2–63.0)	0.0	.	.
IV	27.9 (26.7–29.1)	0.0	25.5 (23.9–27.1)	0.0	31.3 (29.9–32.6)	0.0	.	.
Breast	Denmark		Norway		Sweden		Iceland	
	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp
All	97.0 (96.5–97.4)	.	97.6 (97.0–98.0)	.	97.8 (97.5–98.1)	.	96.0 (93.2–97.6)	.
Missing	92.8 (91.1–94.2)	–0.2	73.4 (63.4–81.1)	–11.8	92.3 (89.6–94.3)	1.2	74.3 (48.6–88.5)	–13.9
0–I	99.9 (93.2–100.0)	–0.6	100.8 (100.8–100.8)	–0.2	100.3 (100.3–100.3)	–0.1	100.9 (100.9–100.9)	–1.0
II	99.0 (98.3–99.5)	–0.8	99.1 (98.2–99.5)	–0.3	98.7 (98.2–99.1)	–0.2	99.0 (87.9–99.9)	–2.3
III	93.5 (91.5–95.1)	–3.2	96.3 (94.3–97.5)	–0.0	92.3 (90.0–94.1)	–0.2	95.3 (78.6–99.1)	–0.1
IV	68.4 (63.5–72.7)	0.0	72.9 (67.6–77.6)	0.0	65.4 (61.3–69.3)	0.0	69.2 (52.3–81.2)	0.0
Kidney	Denmark		Norway		Sweden		Iceland	
	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp	1-year survival	Δ pp
All	84.8 (83.2–86.2)	.	87.4 (85.8–88.8)	.	90.6 (89.5–91.6)	.	.	.
Missing	75.7 (70.2–80.4)	–6.5	83.6 (81.2–85.7)	–0.8	72.1 (58.8–81.8)	–20.4	.	.
0–I	97.4 (95.6–98.4)	–0.7	99.6 (86.7–100.0)	–0.0	100.0 (0.0–100.0)	–0.0	.	.
II	92.4 (86.8–95.7)	–1.3	97.3 (90.0–99.3)	–1.3	96.9 (93.4–98.6)	–0.1	.	.
III	92.5 (88.9–95.0)	–2.1	88.8 (81.9–93.1)	–2.6	95.5 (93.0–97.1)	0.3	.	.
IV	48.4 (43.8–52.8)	–0.1	52.1 (43.4–60.1)	–0.8	55.8 (51.3–60.0)	0.2	.	.

Δ pp percentage point change in relative survival from strict TNM-rules (A1) to application of NOM0 for NXXMX (A3).

The Danish Lung Cancer Group database operates with the concordance between cTNM and pTNM as one of the quality criteria [12]. Another initiative in Denmark influencing TNM availability is the national screening program for colon and rectum cancer implemented in 2014–2017 [13]. Our results showed that the proportions of colon and rectum cases with available TNM stage were about 10 pp lower in Denmark than in Sweden after assuming NOM0 for NXXMX. The decrease in survival for the remaining missing/incomplete group was rather small, less than 3 pp, compared to the other countries which displayed survival decreases of 17–25 pp for colon and 6–10 pp for rectum for the group with missing TNM stage. It appeared that more than 5% of all colon and rectum cases in Denmark were registered with TNM records of TXNXXM0, i.e., not distant metastases, and thus hindering relocation to a specific TNM stage (0–I, II or III) when applying assumptions. This pattern likely coincided with the initiation of the screening program.

The distribution of TNM stage for breast cancer in Sweden differed slightly from the other countries, with a

higher proportion of cases in stages 0–II. Stage 0 was registered in more than 4% of the cases in contrast to very few in the other countries (not shown in tables), and the percentage with stage IV in Sweden was slightly lower than in the other countries. Concomitantly, the overall survival was slightly higher in Sweden, and the stage-specific survival estimates were slightly lower. This may indicate a systematic 'lower stage-assessment' and thus stage-migration in Sweden for breast cancer compared with the other countries. The stage-migration in Sweden was likely due to a high proportion of the reported TNM being based on clinical examination of non-palpable tumors where tumor size was coded as T0 [14].

For colon, rectum, and lung cancer in Norway, the lower proportion of cases with stage IV and the higher proportion with no TNM information might be due to the reporting from the Norwegian clinical/quality databases [8], which primarily is aimed at including patients eligible for surgery, and, further, because TNM registration is not mandatory in Norway.

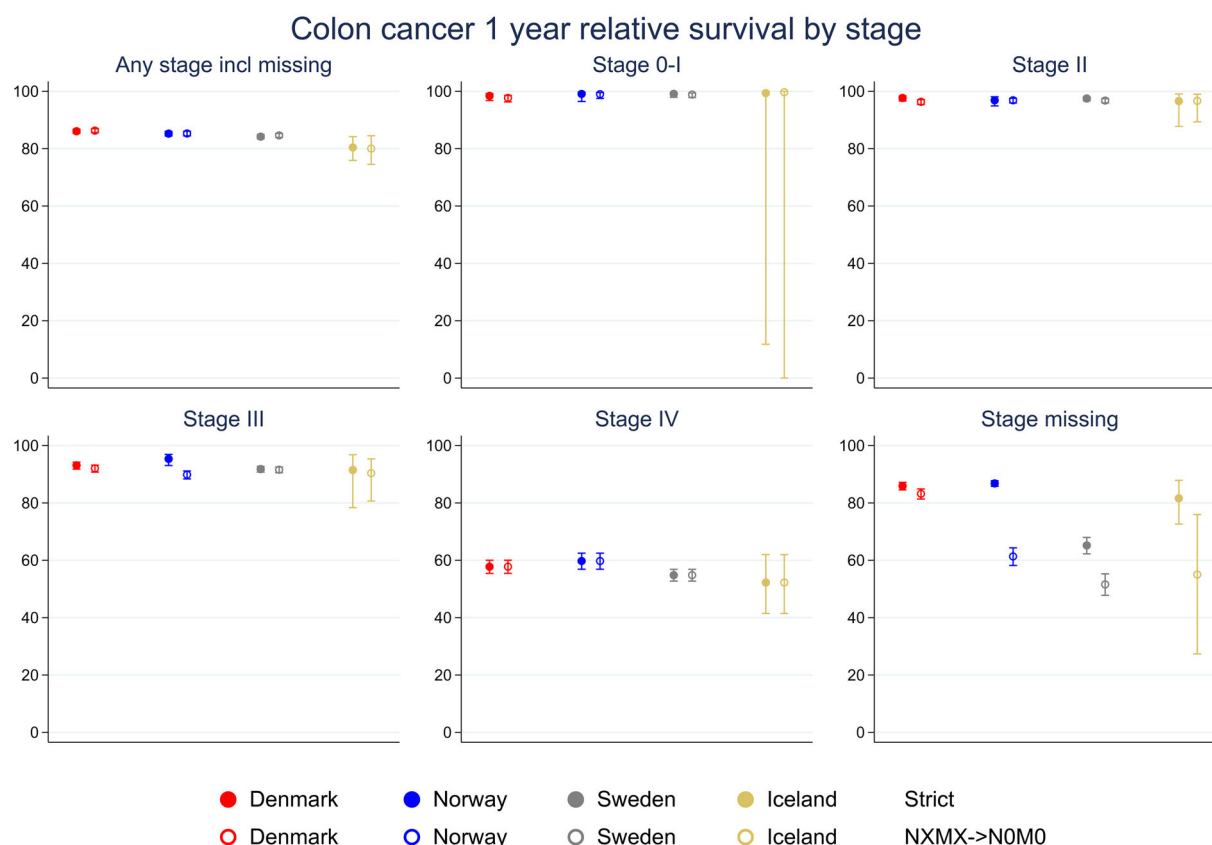


Figure 1. Age-standardised one-year relative survival by TNM stage for colon cancer 2014–2016 according to approach 1 and 3 in Denmark, Norway, Sweden, and Iceland.

Our evaluation of the implications of various assumptions of the individual TNM components on the final TNM stage was prompted by the observation that the proportion of cases with available TNM stage for colon and rectum cancer in Denmark was higher in the SurvMark2 studies than we observed in Denmark when applying the strict approach (A1) [3]. We found that the proportions of cases with missing TNM stage in SurvMark2 for Denmark were comparable to the A3 approach applied for Danish data 2010–2014 (comparison not shown). The SurvMark2 algorithm for converting T, N, and M to TNM stage was derived from a predecessor project to SurvMark2, i.e., ICBP1 [15], differing slightly from the 7th edition of the TNM manual. A report from ICBP1 summarized the experience from comparisons of TNM information for colorectal, lung, breast, and ovarian cancer in six countries during 2000–2007 [16]. According to this report, the ICBP1 study used a ‘restrictive’ approach for handling TNM data before conversion to a ‘SEER2000’ approach with three categories, i.e., localized, regional, and distant stage. This ‘restrictive’ approach was comparable to our strict approach, A1. The SurvMark2 studies included cases for which NXMX was interpreted as N0M0 and thus used as a valid TNM registration, however, the authors did not discuss the change in the stage distribution and the interpretation hereof [3–5].

In addition to the TNM conversion, SurvMark2 also used multiple imputation to estimate the TNM stage for remaining cases with missing TNM. In our study, we found that the

distribution of TNM stage under the A3 approach tended to include more cases from the lower TNM stage categories and the TNM stage-specific survival also tended to decline, as illustrated in Figure 1 for colon cancer. A similar pattern may also appear after imputation and might compromise comparisons of TNM stage distribution and stage-specific survival between countries.

Strength of the study

The study was based on large national cohorts from four nationwide cancer registries. The Nordic cancer registries have a long history of collaboration since the 1950s and the registry data have contributed to numerous projects aiming to coordinate and describe cancer trends and to develop new tools for improved statistics to support cancer surveillance. The NORDCAN database represents a key data source for such initiatives. The ambition behind our study was to facilitate that TNM as recorded in the cancer registries becomes a key statistic in future surveillance studies as well as empirical epidemiological and clinical studies. Registration of TNM has been mandatory in Denmark and Sweden from 2004 while TNM registrations in the Norwegian Cancer Registry rely on voluntary information in notifications to the cancer registry supplemented by registrations in newly established clinical registries. Although TNM-stage is based on manuals with a precise description of how to code each of the TNM components, as well as how to combine the

components to a final TNM stage (1), the reporting and registration of TNM is still not satisfactory. Considering that TNM is a key predictor of cancer prognosis, clinicians should be urged to improve the reporting of TNM information to the cancer registries.

Study limitations

We only studied one-year relative survival although further effects on survival might occur later, e.g., five or ten years after diagnosis. The sensitivity analysis comparing TNM stage distributions between approach A3-path (preference of pTNM above cTNM) to our approach A3 (maximum of T, N, and M from cTNM and pTNM) revealed the largest change for rectum cancer in Iceland where the A3-path approach might have been more appropriate and resulted in a more comparable stage distribution to the other countries. We chose the approach with the highest T, N, and M from cTNM and pTNM *à priori* according to the approach used in the Danish Cancer Registry. For the strict approach (A1) this yielded more comparable TNM stage distributions between countries.

Conclusion

We found no major changes in stage-specific one-year relative survival applying N0M0 for NXMX, especially for high TNM-completeness. Thus, it seems reasonable to consider the implementation of this algorithm in future studies based on the Nordic cancer registries, but default use of the algorithm is not recommended for a specific site without gathering information on any specific reasons for frequent use of NX and MX in a given country or region while still acknowledging that differences might be found for longer follow-up. However, complete information is preferable to making assumptions and therefore we recommend that clinicians should be urged to report complete TNM information to the cancer registries to improve surveillance of stage information, in particular since the TNM stage is a crucial indicator for survival.

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Ethical approval

For register-based studies, ethical approval is not relevant in the Nordic countries.

Author contributions

GE: Conceptualization, Data curation, Formal analysis, Methodology, Writing-Original draft preparation, Writing-Reviewing, and Editing. FEL: Formal analysis, Methodology, Writing-Reviewing, and Editing. SMK: Writing-Reviewing and Editing. EÖ: Writing-Reviewing and Editing. TBJ:

Writing-Reviewing and Editing. DP: Writing-Reviewing and Editing. LSM: Writing-Reviewing and Editing. ALVJ: Methodology, Writing-Reviewing, and Editing. SF: Methodology, Writing-Reviewing, and Editing. The work reported in the paper has been performed by the authors unless clearly specified in the text.

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Data availability statement

Individual person information is not freely available due to GDPR legislation. Tabulated data for the cases included (Sex, age, cancer site, year of diagnoses, country but not TNM) can be seen in the publicly available Nordic cancer statistics database NORDCAN, <https://nordcan.iarc.fr/en>. Application for access to individual data from each of the countries can be made to the National Cancer Registries in Denmark, Norway, Sweden, and Iceland.

References

- [1] Brierley JD, Gospodarowicz MK, Wittekind C, eds. TNM classification of malignant tumours. 8th ed. Oxford: Wiley-Blackwell; 2017. p. 253.
- [2] Kerr DJ, Haller DG, van de Velde CJH, et al. eds. Oxford textbook of oncology. 3th ed. New York (NY): Oxford University Press; 2016.
- [3] Aragli M, Arnold M, Rutherford MJ, et al. Colon and rectal cancer survival in seven high-income countries 2010–2014: variation by age and stage at diagnosis (the ICBP SURVMARK-2 project). *Gut*. 2021;70(1):114–126.
- [4] Arnold M, Morgan E, Bardot A, et al. International variation in oesophageal and gastric cancer survival 2012–2014: differences by histological subtype and stage at diagnosis (an ICBP SURVMARK-2 population-based study). *Gut*. 2022;71(8):1532–1543.
- [5] Aragli M, Fidler-Benaoudia M, Arnold M, et al. International differences in lung cancer survival by sex, histological type and stage at diagnosis: an ICBP SURVMARK-2 study. *Thorax*. 2022; 77(4):378–390.
- [6] Sobin LH, Gospodarowicz MK, Wittekind C, eds. TNM classification of malignant tumors. 7th ed. Chichester: Wiley; 2009. p. 310.
- [7] Pukkala E, Engholm G, Højsgaard Schmidt LK, et al. Nordic cancer registries - an overview of their procedures and data comparability. *Acta Oncol*. 2018;57(4):440–455.
- [8] Nilbert M, Thomsen LA, Winther Jensen J, et al. The power of empirical data; lessons from the clinical registry initiatives in Scandinavian cancer care. *Acta Oncol*. 2020;59(11):1343–1356.
- [9] Perme MP, Stare J, Estève J. On estimation in relative survival. *Biometrics*. 2012; 68(1):113–120.
- [10] Sasieni P, Brentnall AR. On standardized relative survival. *Biometrics*. 2017;73(2):473–482.

- [11] Rutherford MJ, Dickman PW, Coviello E, et al. Estimation of age-standardized net survival, even when age-specific data are sparse. *Cancer Epidemiol.* 2020;67:101745.
- [12] Jakobsen E, Rasmussen TR. The Danish Lung Cancer Registry. *Clin Epidemiol.* 2016;8:537–541.
- [13] Cardoso R, Guo F, Heisser T, et al. Colorectal cancer incidence, mortality, and stage distribution in european countries in the colorectal cancer screening era: an international population-based study. *Lancet Oncol.* 2021;22(7):1002–1013.
- [14] Lundberg FE, Kroman N, Lambe M, et al. Age-specific survival trends and life-years lost in women with breast cancer 1990–2016: the NORDCAN survival studies. *Acta Oncol.* 2022;61(12):1481–1489.
- [15] Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet.* 2011;377(9760):127–138.
- [16] Walters S, Maringe C, Butler J, et al. Comparability of stage data in cancer registries in six countries: lessons from the International Cancer Benchmarking Partnership. *Int J Cancer.* 2013; 132(3):676–685.