Concordance between clinical and pathology TNM-staging in lung cancer

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ABSTRACT

Objectives: A prerequisite for utilizing the tumour, lymph-nodes, and metastases (TNM) for the staging of lung cancer patients is a high quality of the reported data on which the staging is based. The aim of this study was to investigate the concordance between the clinical, cTNM and the pathology, pTNM staging for lung cancer, version 8 as reported to the Cancer Registry of Norway (CRN).
Materials and Methods: A total of 1284 patients who underwent surgery 2018–2019 with sufficient data regarding both clinical and pathology T and N descriptors were included.
Results: The differences in tumour diameter reported in the clinical and the pathology notifications were ≤5 mm and ≤10 mm in 65.9 % and in 84.4 % of the cases, respectively. For the c- and pT categories, there was concordance in 53.4 % while 28.4 % were upstaged and 18.2 % were downstaged. For N categories there was concordance in 83.3 % while 13.7 % were upstaged and 3.0 % were downstaged. Unforeseen pN2 was found in 6.2 % of the cases. For TNM staging groups there was concordance in 48.1 % of the cases, while 33.4 % were upstaged and 18.5 % were downstaged. The calculated sensitivity and specificity for reported cTNM staging as diagnostic test for being eligible for adjuvant treatment (stage II–IIIA) were 0.65 and 0.91, respectively.
Conclusions: These data on staging for lung cancer, as reported to the CRN, shows a disappointingly low precision and concordance in c- and pTNM staging. This urges a strategy for a marked improvement.

1. Introduction

Staging based on tumour characteristics (T), lymph node engagement (N) and metastases (M) – the TNM system is an important tool for treatment planning, outcome evaluation, estimating prognosis, and research. The 8th version for lung cancer, TNM-8 was introduced in 2017 [1]. The staging quality is of particular importance where staging defines treatment as for adjuvant therapy in patients staged II-IIIA [2].

National data on staging quality has been presented from Denmark [3] and the Netherlands [4]. The annual reports from the quality register

for lung cancer in The Cancer Registry of Norway CRN [5,6] indicated that the present Norwegian data was unsatisfactory, and advocated a study of the underlying data causing the lack of concordance between c- and pTNM.

In Norway, virtually all cancer patients are diagnosed and treated in a public health care system. Of the patients with lung cancer, 98.8 % were reported to CRN [7]. A more detailed quality register for lung cancer launched in 2013, comprises modules for biopsy, medical treatment, radiotherapy, diagnostics, surgery, and morphologic description of the surgical specimens. The present study was based on data from the

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diagnostic and the pathology notifications from the surgical specimens. The CRN is based on Norwegian law, so no specific approval is needed for analysing and presenting data on a group basis.

The aim of this study was to investigate the concordance between clinical and pathology staging, and underlying descriptors in patients operated for lung cancer in Norway in 2018–2019.

2. Materials and methods

In 2018–2019, a total of 1447 (21.9 % of those diagnosed) patients were reported to CRN as operated for lung cancer. Of these, 1375 (95.0 %) were registered with both diagnostic- and pathology notifications, and 1284 (88.7 %) could be completely staged by both c- and pTNM. Missing, incomplete or unprecise data for complete, staging was the reason for exclusion. Exact data for tumour diameter and date of sending of both clinical- and pathology notifications were available in 1277 cases, enabling evaluation of concordance in measuring diameter and the influence whether the pathology data was available at the time of sending the clinical notifications. The differences were calculated as the diameter in millimetres reported in the clinical- minus the diameter in the pathology notification. The mean time from diagnosis to surgery was 32.4, SD 38.4 days.

The characteristics of the patient group are shown in Table 1. The female predominance (54.2 %) in the whole group was significant (p = 0.001). The increased proportion of males in the higher stages was significant (p < 0.001).

2.1. Statistical analysis

For comparison of groups, Pearson chi square test or *t*-test was used. For comparing proportions, Fisher's exact test and test of proportions were used. Logistic regression was used for analysing stage as outcome and sex and age as predictors. All analyses were done in Stata (Ver. 17.0, StataCorp, Texas, USA).

Table 1
Characteristics of the surgical population diagnosed 2018–2019, based on the diagnostic notifications.

	n (%)	
Total	1375	
Females	745 (54.2)	
Age (mean/SD/median/min–max) years	67.7/9.0/69/17–88	
Adenocarcinoma	717 (52.2)	
Squamous cell carcinoma	270 (19.6)	
Small cell carcinoma	21 (1.5)	
NSCLC-NOS	44 (3.2)	
Carcinoid tumour	91 (6.6)	
Other	35 (2.6)	
Unknown/missing histology	197 (14.3)	
Preoperative procedures		
CT scan	1375 (100.0)	
CT scan with cytology/biopsy	882 (61.4)	
PET-CT	1307 (95.1)	
Bronchoscopy	468 (34.0)	
Bronchoscopy with biopsy of tumour	229 (16.7)	
EBUS-FNAC	259 (18.8)	
Mediastinoscopy with biopsy	7 (0.5)	
	Females	Males
Clinical stage I	533 (58.3)	381 (41.7)
Clinical stage II	120 (44.9)	147 (55.1)
Clinical stage III	67 (42.1)	92 (57.9)
Clinical stage IV	11 (68.8)	5 (31.3)

3. Results

3.1. Tumour size

The mean difference in tumour diameter was −0.1 mm, median 0, SD 12.2 mm. For the 563 cases with negative differences (pathology diameter the largest), the mean was −7.24 mm (SD 7.90) and the median was − 5 mm. For the 504 with positive differences the mean was −7.95 mm (SD 13.64) and the median was 4 mm. Fig. 1 shows a divergence between the curves whether the diagnostic- or pathology notification was sent first in the difference interval 5–11 mm. In this interval, the diameter in the diagnostic notifications for the 171 cases had a mean of 37.5 mm which was significantly higher than the mean diameter 29.8 mm (p > 0.001) in the remaining cases. Thus, there was a significant downsizing in the subgroup of patients with a large preoperative diameter.

In the reporting of the tumour diameter, 381 (29.8 %) of the clinical and 488 (38.2 %) of the pathology notifications used zero or five as the terminal digit, respectively. By test of proportions, assuming the correct proportion was 20 %, the observed clustering was significantly increased (p < 0.001 for both).

In the 752 cases where the pathology notification was sent first, a marked and significant increase was observed in zero difference in diameter compared to the cases where the diagnostic notifications were sent first (Fig. 1, Table 2). The mean of the absolute values of the differences in size was significantly increased in the cases where the diagnostic notifications were sent first (Table 2). The proportion of all cases where the sum of the differences was ≤5 mm and ≤10 mm was 65.9 % and 84.4 % respectively.

The absolute difference in diameter was ≤5 mm in 318 cases (60.6 %) when the diagnostic notification was sent first and 524 (69.7 %) when the pathology notification was sent first (p < 0.001).

3.2. Tumour categories

The correlation between cT and pT categories (Table 3) revealed concordance in 686 (53.4 %) cases, while 364 (28.4 %) were upstaged and 234 (18.2 %) downstaged.

For the different cT categories, the proportion of concordance varied from 39.2 % in category 1a to 67.8 % in category 4. When condensing the staging to the four main *T*-categories (1–4) there was concordance in 904 (70.4 %), upstaging in 240 (18.7 %) and downstaging in 140 (10.9 %).

For descriptors as whether the tumour has infiltrated the visceral pleura or involved the chest wall, the sensitivity, using c- as the diagnostic test and p- as gold standard, was 0.20 and 0.23, and the specificity 0.95 and 0.99, respectively.

3.3. Lymph node categories

The correlation between cN and pN (Table 4) revealed concordance in 1069 (83.3 %), upstaging in 176 (13.7 %) and downstaging in 39 (3.0 %). For the different cN categories, the proportion of concordance varied from 59.8 % in cN1 and 60.0 % in cN2, to 86.4 % in cN0.

Of 107 cases categorized as pN2, 27 had been diagnosed as cN2, while 80 cases (6.2 % of the total cohort) had an unforeseen pN2. Of the 45 cases diagnosed as cN2, 27 (53.3 %) were confirmed as pN2. The number of cases reported as cN0 was 1139 (88.7 %), pN0 was 1017 (79.2 %) and both c- and pN0 was 984 (76.6 %).

3.4. TNM stage

Concordance between cTNM and pTNM stage (Table 5) was found in 618 (48.1 %) cases, while 429 (33.4 %) were upstaged and 237 (18.5 %) were downstaged. For the different cTNM stages, the proportion of concordance varied from 25.0 % in category cIIIB to 62.0 % in category
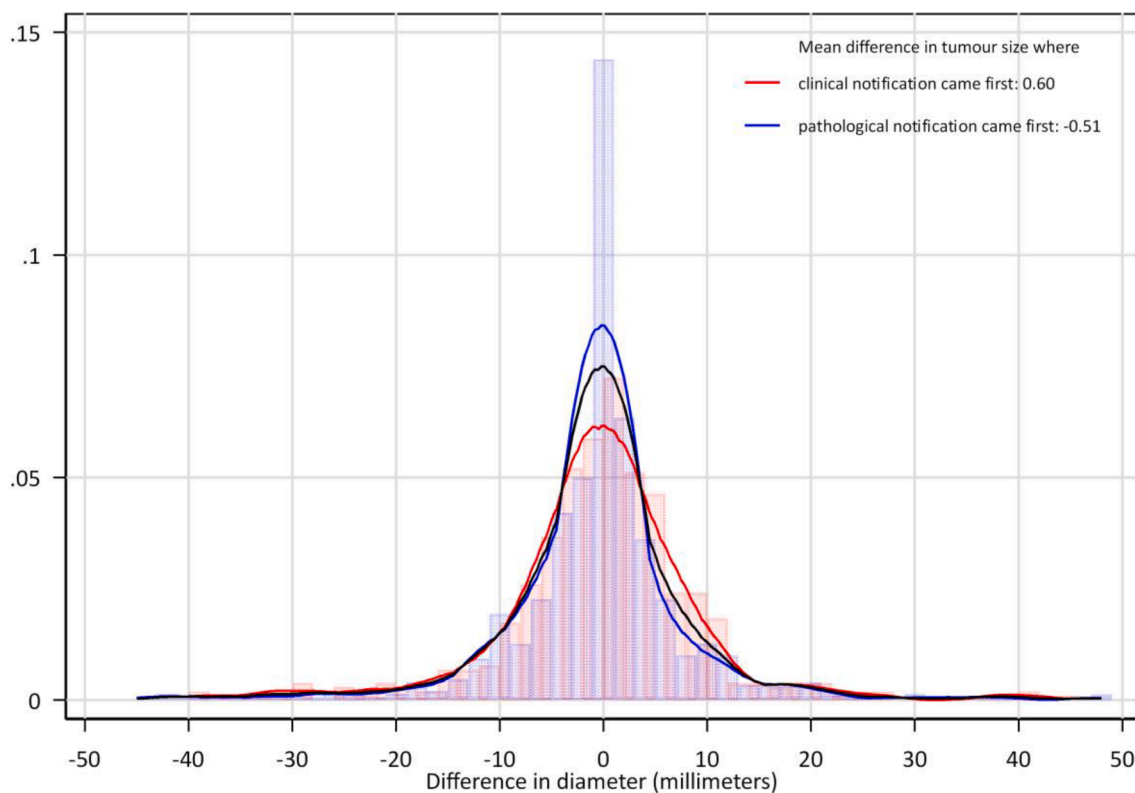
Fig. 1. The difference between tumour size - diameter as noted in the diagnostic and pathology notifications. The differences are calculated as the diameter reported in the diagnostic notification minus the diameter measured in the resected specimens. The black curve shows the distribution for all 1277 cases. The blue bars and curve show the distribution for the 752 cases where the pathology notifications were sent first, and the red shows the distribution for the 525 cases where the clinical notifications were sent first. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of absolute differences in the tumour diameter (in millimetres). Both total and separated by the order the notifications were sent to the CRN.

	N	Zero difference	Correlation	Mean	Sd	Median	≤5 mm[#]	≤10 mm
Total	1277	210 (16.4 %)	0.8154	6.3	10.4	3	842 (65.9 %)	1078 (84.4 %)
Clinical first	525 (41.1 %)	43 (8.2 %)[#]	0.7478	7,6*	13.0	4	318 (60.6 %)[#]	435 (82.9 %)
Pathology first	752 (58.9 %)	167 (22.2 %)[#]	0.8727	5.4*	8.0	3	524 (69.7 %)[#]	643 (85.5 %)

*p = 0.001, *t*-test.
[#] p < 0.001, Fisher's exact test.

Table 3
The correlation between cT and pT categories, all cases†.

cT	pT							Total
	1a	1b	1c	2a	2b	3	4	
1a	40 (39.2)	42	6	11	0	2	1	102
1b	24	234 (64.1)	39	51	3	13	1	365
1c	3	45	101 (41.1)	82	5	11	0	246
2a	3	18	45	124 (49.6)	37	19	4	250
2b	1	0	4	22	55 (52.9)	21	1	104
3	0	6	4	16	16	73 (56.2)	16	130
4	1	5	1	4	5	12	59 (67.8)	87
Total	72	350	200	308	121	151	82	1284

†The shaded boxes show the number of cases with concordance between cT and pT. The percentage concordance is in the brackets. There is upstaging for the cases above the shaded diagonal and downstaging below.

cIA2. In 529 (41.2 %) cases where the clinical notifications were sent first, the concordance was significantly lower (p < 0.001) than in the 401 (53.1 %) cases in the group with where the pathology notifications were sent first.

When condensing to the four main stages (I – IV) there was concordance in 971 (75.6 %) cases, upstaging in 218 (17.0 %) and downstaging in 95 (7.4 %).

There was concordance in 308 cases between the cTNM and pTNM

Table 4
The correlation between cN and pN categories, all cases†.

cN	pN				Total
	0	1	2	3	
0	984 (86.4)	95	59	1	1139
1	18	58 (59.8)	21	0	97
2	12	6	27 (60.0)	0	45
3	3	0	0	0	3
Total	1017	159	107	1	1284

†The shaded boxes show the number of cases with concordance between cT and pT. The percentage concordance is in the brackets. There is upstaging for the cases above the shaded diagonal and downstaging below.

for stage II–IIIA, eligible for adjuvant chemotherapy. There were 381 cases diagnosed with cTNM II–IIIA of which 23 (6.0 %) were upstaged and 50 (13.1 %) were downstaged. In pathology, 482 cases were classified as stage II–IIIA, of which 159 (33.0 %) were upstaged and 15 (3.1 %) were downstaged. The calculated sensitivity and specificity for c-staging as diagnostic test in this group were 0.65 and 0.91, respectively.

In 529 (41.2 %) cases where the clinical notifications were sent first, there were concordance in 219 (41.4 %) cases which was significantly lower (p < 0.001) than in the 401 (53.1 %) cases in the group where the pathology notifications were sent first.

Neoadjuvant therapy was given in 16 (1.2 %) of the cases, and in 72 (5.6 %) cases more than one tumour was diagnosed. These cases had a negligible effect on the concordance.

4. Discussion

The present study, based on national data shows a disappointingly low concordance (48.1 %) between c- and pTNM. This was mainly caused by low concordance in T categories, which may be artificially improved probably due to copying tumour diameter from pathology into the clinical notifications when these were sent after the pathology notifications. Further, the significantly increased clustering of zero or five as terminal digit for tumour diameter may indicate that too little effort was made to report the exact diameter both clinically and in pathology. The results could be disturbed by patients given neoadjuvant therapy, or with more than one tumour, but both were few and their impact on the staging was negligible.

An area of particular importance for good staging is allocating patients to correct treatment. For patients staged II-IIIA adjuvant chemotherapy is advised [2]. Also, in this group the concordance was low.

The absolute differences in tumour diameters in our study was ≤5 mm in 65.9 %, thus, in 34.1 % the difference in tumour diameter was >5 mm and may induce stage migration in a marked proportion of the cases. In most of the cases where the difference was >10 mm (15.6 %) there would be a stage migration. In comparison of the diameter of the

tumours given in the diagnostic and pathology notifications, the difference had a high degree of accuracy as the figures were evenly distributed on each side of zero difference. Except for downstaging a subset of larger tumours there were no systematic up- or downstaging of tumour diameter. The precision however was disappointingly low. None of these descriptors as infiltrating the pleura or chest wall had a satisfactory combination of specificity and sensitivity.

There has been a slight drifting away from considering cN2 as an absolute contraindication for surgery. However, a thorough preoperative assessment of the mediastinal lymph nodes is mandatory. Few decisions for surgery are based on TNM staging alone, but still a good staging is important as guidance. Stereotactic body radiation can be offered a subset of patients with cN0, but a low proportion of patients with a comprehensive examination of the lymph nodes increase the risk of making wrong decisions.

In addition to being retrospective, one weakness of the present study is that Nx was not used in staging, and category N0 was used even when no lymph nodes were examined. Table 4 shows acceptable concordance between cN and pN, and the proportion unforeseen pN2. In addition, when not using Nx, a low proportion of EBUS and a very low proportion of mediastinoscopies (Table 1) indicates a too high proportion diagnosed as cN0. Also, a mean of 3.0 lymph nodes excised in surgery [6] is not in line with international and national guidelines [8,9]. The acceptable concordance for the N categories was thus mainly a result of the artificially high number and concordance (86.4 %) in cN0 and pN0. The concordance for cN1 and N2 at 59.8 % and 60.0 % respectively probably reflect the quality of the N-staging more truly. A strength of this study is the completeness of the registrations of national data in the CRN [6]. Also, in spite of the low concordance in staging, a high proportion of the patients has been given treatment with curative intention [6], and the 5 year relative survival for all diagnosed with lung cancer is high and has increased from 9.4 % in 2001 [10] to 25.9 % in 2019 [5] and 27.2 % in 2020 [6].

The detailing in TNM staging can be developed to the near impeccable but must be practiced in a reality where precise staging and reporting may come second to the daily clinical work.

5. Conclusion

The present study shows unsatisfactory concordance in the reported data between clinical and pathology staging of lung cancer. Improving this is a necessary task for both the professional bodies, the CRN, and the health authorities. The CRN has started by including the concordance for each hospital in the annual report for 2021. A further refinement from TNM-8 may be futile unless the quality of the staging is improved.

Table 5
The correlation between cTNM and pTNM stages, all cases†.

cTNM	pTNM										SUM
	IA1	IA2	IA3	IB	IIA	IIB	IIIA	IIIB	IVA	IVB	
IA1	39 (39.8)	39	6	8	0	4	2	0	0	0	98
IA2	23	209 (62.0)	30	39	2	22	10	1	1	0	337
IA3	3	42	83 (36.3)	53	5	31	10	0	0	0	227
IB	3	16	34	77 (36.5)	23	33	17	8	0	0	211
IIA	0	0	3	13	41 (47.1)	23	3	4	0	0	87
IIB	0	2	4	13	13	88 (54.3)	36	5	1	0	162
IIIA	2	5	1	7	4	23	77 (58.3)	13	0	0	132
IIIB	0	2	0	0	1	1	8	4 (25.0)	0	0	16
IVA	0	1	3	5	0	3	1	0	0	0	13
IVB	0	0	0	0	1	0	0	0	0	0	1
SUM	70	316	164	215	90	228	164	35	2	0	1284

†The shaded boxes show the number of cases with concordance between cTNM and pTNM. The percentage concordance is in the brackets. There is upstaging for the cases above the shaded diagonal and downstaging below.

CRediT authorship contribution statement

Steinar Solberg: Investigation, Conceptualization, Methodology, Writing – original draft. **Yngvar Nilssen:** Conceptualization, Software, Visualization. **Odd Terje Brustugun:** Conceptualization. **Per Magnus Haram:** Data curation, Conceptualization. **Åslaug Helland:** Funding acquisition, Conceptualization. **Bjørn Møller:** Data curation, Conceptualization, Software. **Trond-Eirik Strand:** Data curation, Conceptualization. **Sissel Gyrid Freim Wahl:** Data curation. **Lars Fjellbirkeland:** Data curation, Supervision.

Declaration of Competing Interest

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