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Are survival predictions reliable? Hospital volume versus standardisation of histopathologic reporting for accuracy of survival estimates after pancreatoduodenectomy for adenocarcinoma

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ABSTRACT

Histopathologic reporting after pancreatoduodenectomy is often non-standardised. Inappropriate reporting may bias survival estimates and make comparison between institutions difficult. Using population-based nationwide data from the Cancer Registry of Norway, we examined the influence on survival estimates of standardised histopathologic reporting versus non-standardised histopathologic reporting after pancreatoduodenectomy for adenocarcinomas in the pancreas, distal bile duct, ampulla and duodenum ($n = 506$). Standardised histopathologic reports from a study hospital ($n = 113$) were compared with reports from all other institutions (24 hospitals; $n = 393$) discriminating between high/medium-volume and low-volume institutions. In the study hospital, more tissue blocks were sampled, more nodes were evaluated, and more details about resection margins, size, origin and vascular and perineural infiltration were reported ($p < 0.001$). Multivariable survival analysis identified lymph node involvement as the factor that is most dependent on standardised reporting to discriminate between favourable and poor prognostic subgroups ($p = 0.018$). Standardised evaluation was more important than hospital volume for completeness of histopathologic reporting and for accuracy of survival estimates.

1. Introduction

Adenocarcinomas in the pancreatic head are most often non-resectable, and even when curative-intent resection is performed, most patients die within a few years.[1,2] Adjuvant treatment trials on advanced and resected pancreatic cancer have shown only limited effect,[3] and new treatment options are urgently needed.[4] In order to translate laboratory research findings into clinical practice, the first step should be to ascertain that information on histopathologic prognostic factors is available for every resected patient, and is recorded in a way that facilitates comparability between groups of patients.

In spite of many efforts to standardise assessment of pancreatoduodenectomy specimens,[5–15] histopathologic report-

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ing after pancreatic head resections is frequently non-standardised,[13–15] even in multicentre studies.[16] Non-standardised reporting could lead to underestimation of the presence of poor prognostic factors such as resection margin involvement[13] and regional lymph node metastasis,[17] due to lack of systematic investigation of the resected specimen. Failure to recognise resection margin or lymph node involvement would in turn negatively skew survival estimates for allegedly margin-free or node-free resected patients. Moreover, the precise tumour origin of adenocarcinomas resected by pancreatoduodenectomy (pancreatic, ampullary, distal bile duct or periampullary duodenal) may be difficult to determine.[7,14,18–23] Inclusion of prognostically more favourable, non-pancreatic tumours in reports of pancreatic head resections could thus skew survival estimates in a positive direction.[24,25] Standardisation of histopathologic evaluation should be an effective measure to increase the quality of histopathologic reporting, and also ensures adequate inclusion and stratification for clinical trials.

The direct impact on accuracy of survival estimates derived from standardised histopathologic reporting versus non-standardised histopathologic reporting of solid cancers to our knowledge has not been evaluated previously, using population-based nationwide data comparing the independent importance of each factor reported. The aim of this study was to evaluate whether standardised histopathologic reporting after curative-intent pancreatoduodenectomy for adenocarcinoma improves the registration of the prognostic factors tumour size, lymph node involvement, resection margin involvement, and tumour origin (pancreatic, ampullary, distal bile duct or duodenal), adjusting for importance of surgical volume. Furthermore, we wanted to assess the consequences for survival estimates based on these factors comparing standardised reporting versus non-standardised reporting.

2. Patients and methods

2.1. Patients

The Cancer Registry of Norway receives mandatory reports on all cases of cancer diagnosed or treated in Norway (population 4.6 million in 2004).[26,27] By law and according to the Cancer Registry Regulations, data on verified and suspected cancers are collected from all hospitals and pathology institutions and are made available for researchers as deidentified files. From the Cancer Registry, 506 patients who underwent curative-intent pancreatoduodenectomy for pancreatic head adenocarcinoma in Norway from 1998 to 2004, inclusive, were identified. For each patient, the following information was electronically retrieved from the Cancer Registry: age, gender, date of surgery and the anatomic site of cancer origin. One patient was diagnosed with two separate adenocarcinomas in the pancreatic head, originating from the ampulla and the pancreas, respectively. For the purpose of the current study, this patient was classified as having a single tumour originating from the pancreas.

Among the 506 pancreatoduodenectomies for adenocarcinomas, 113 were performed at the study hospital, a third-level referral hospital with standardised histopathologic assessment and reporting of pancreatoduodenectomy specimens.[14] Basis for standardised reporting at this hospital included the use of a standardised protocol for gross examination, specimen dissection, tissue sampling and microscopic assessment. The template that is currently used for summarising the most important histopathologic findings

DIAGNOSIS
PANCREATODUODENECTOMY SPECIMEN WITH
WELL / MODERATELY / POORLY / ANAPLASTIC DIFFERENTIATED ADENOCARCINOMA OF
PANCREATOBILIARY / INTESTINAL / _____ (other) HISTOLOGIC TYPE
ORIGINATING FROM THE **PANCREAS / DISTAL BILE DUCT / AMPULLA VATERI / DUODENUM**
WITH INFILTRATION INTO THE **PANCREAS / DISTAL BILE DUCT / AMPULLA VATERI / DUODENUM**

Extent of tumour growth
Tumour size (largest diameter): **____mm**
Resection margin, distal bile duct: **free by minimum ____ mm / involved**
Resection margin, pancreatic neck: **free by minimum ____ mm / involved**
Resection margin, retroperitoneal (posterior): **free by minimum ____ mm / involved**
Involvement of large vessels: ____ (Resection margin: **free by minimum ____ mm / involved**)
Infiltration to anterior (serosal) margin: **detected / not detected**
Infiltrasjon to stomach: **detected / not detected**

Nodal involvement
Regional lymph nodes: **____ positive**. Total number of regional nodes evaluated: ____
Other lymph nodes: **____ positive** in _____ (location). Total number of other nodes evaluated: ____

Other histopathologic characteristics
Small-vessel involvement: **detected / not detected;** in **blood / lymph** vessels
Perineural involvement: **detected / not detected**
PanIN, **grade ____ detected / not detected** (in pancreatic ducts)
BilIN, **grade ____ detected / not detected** (in biliary ducts)

pTNM (dependent on tumour origin): ____

Additional pathology

Fig. 1 – Template for standardised histopathologic reporting of pancreatic head adenocarcinoma specimens that is currently used at Rikshospitalet University Hospital (study hospital). In addition to the diagnosis and conclusion reported using this template, the histopathologic reports consist of a gross description that may include macroscopic photos, and a specific report on the microscopic examination for each block.

is shown in Fig. 1. The template was subjected to various minor improvements during the study period, reflecting increasing knowledge about the pathology of these carcinomas. PanIN classification was, for example, included in late 2001, coinciding with the first publications introducing this new nomenclature.[28] A total of 161 pancreatoduodenectomies were performed at the study hospital during these seven years, of which 39 resections were due to diagnoses other than primary adenocarcinomas. By comparing the list of patients from the applied search in the Cancer Registry with a previously acquired list of pancreatoduodenectomies at the study hospital,[14] nine missing cases were identified, for which histopathologic reports had not been received at the Cancer Registry. Three of these patients were, however, identified in the Cancer Registry with a biopsy-verified pancreatic head adenocarcinoma, and additionally three patients were diagnosed with adenocarcinomas based on diagnostic imaging. In addition, two patients were registered with precancerous changes, while only one patient was completely missing from the Cancer Registry. Nine patients resected at the study hospital were thus missed by the applied search strategy for inclusion of patients into this study. To avoid bias due to possible missing reports also from other institutions, these identified missing patients from the study hospital were not included in the study.

In addition, 24 other hospitals in Norway, with various standards for histopathologic reporting, performed pancreatic head adenocarcinoma resections during this 7-year period. There were no national or regional guidelines for standardisation of histopathologic assessment and reporting during the study period. Specific information on histopathologic assessment (e.g. specimen dissection and tissue sampling) at these hospitals was not collected. Histopathologic reporting and survival estimates from resections performed at the study hospital were compared with medium- and low-volume institutions, which we defined as institutions performing $\geqslant 40$ and <40 primary adenocarcinoma resections during the study period, respectively. Three hospitals, which were also third-level academic institutions with no particular selection bias compared to the study hospital, were thus classified as medium-volume institutions (94, 80 and 47 adenocarcinoma resections, respectively), while the remaining 21 hospitals were classified as low-volume institutions (median 3 adenocarcinoma resections; range 1–35). All resections performed at the study hospital or medium-volume hospitals were reported from the same institutions that performed the pancreatoduodenectomy, while four (of 172) resections at low-volume institutions were reported from one of the medium-volume institutions (the number of specimens evaluated at the three medium-volume institutions was thus 95, 82 and 48 specimens, respectively).

Included cases comprised all identified patients that were resected by pancreatoduodenectomy due to primary pancreatic head, distal bile duct, ampullary and duodenal carcinomas. It should be noted that evaluation of the probable origin is highly dependent on the level of histopathologic standardisation.[14,23,29] To avoid possible reporting bias due to variable levels of expertise between institutions in recognising more uncommon histologic variants such as invasive IPMN, adenosquamous carcinoma, undifferentiated carcinoma and undifferentiated carcinoma with osteoclast-like giant cells, these histologic types were also included (11 of 506). Similar results were, however, obtained when tumours registered with such more uncommon histologic types were excluded. Endocrine tumours, non-epithelial primary tumours, secondary tumours, benign lesions, distal pancreas resections and total pancreatectomies were all excluded.

Survival and migration status were obtained from the National Population Registry. All Norwegian inhabitants receive a unique personal identification number, enabling near complete follow-up of patients. In the present study, no patients were lost to follow-up. Patients were followed until death or 5 years of follow-up (mean follow-up for survivors 4.7 years, range 3.4–5.0 years; survival status checked May 1, 2008). During the study period, adjuvant treatment was not recommended as routine practice.[30] Perioperative death was defined as death within 30 d of operation and was included in all reported survival analyses (study hospital, 3 deaths; medium-volume institutions, 11 deaths; low-volume institutions, 13 deaths). Exclusion of perioperative death gave very similar results.

2.2. *Review of histopathologic reporting*

The following information was retrieved by careful review of all available information in the histopathologic reports: Tumour size (maximum diameter), discriminating between whether the estimation of tumour size was reported in the final conclusion, or in the macroscopic or microscopic description section of the histopathologic report; resection margin involvement (R status, defining R1 as tumour growth closer than 1 mm from a resection margin); regional lymph node involvement (registering also the total number of regional lymph nodes examined and the number of positive regional lymph nodes).

The depth of detail and level of standardisation in histopathologic reporting was further evaluated and compared between reporting institutions by registering the number of blocks sampled, and by registering whether each of the following prognostic factors were reported in the diagnosis or final conclusion of the reports: a statement regarding pTNM-classification, a statement or discussion about the probable tumour origin and whether the tumour origin statement was accompanied by a description of the pattern of infiltrative growth relative to adjacent structures, and whether there was a presence of precancerous changes such as dysplasia (including PanIN and BilIN) or an adenoma component to support the assessment of tumour origin. Furthermore, the conclusion was evaluated for details of possible resection margin involvement, i.e. whether margins were sufficiently specified (defined as a minimum to include the pancreatic neck, the distal bile duct and the retroperitoneal margins), partially specified (defined as 1–2 margins mentioned) or not specified. Finally, we registered whether the conclusion described the histologic type and the grade of differentiation, and whether there was a presence of vascular or perineural involvement. All registrations were based solely on the histopathologic reports retrieved from the Cancer Registry and thus did not include reclassification of prognostic factors

based on reevaluation of microscopic slides at the study hospital[14] or at other institutions.

2.3. Statistical analysis

Histopathologic reporting and time to overall death after surgical resection were compared between the study hospital and other institutions. Associations between variables were examined using Chi-square test, Fisher's exact test and Mann–Whitney test. Unadjusted survival analysis was performed using the Kaplan–Meier method, by comparing curves using log-rank test. Multivariable Cox regression analysis was used for adjusted survival analysis. The proportional hazards assumption was tested graphically. For all comparisons by type of institution, the study hospital was compared with all other institutions. The p-value for the difference in the effect of a prognostic factor between study hospital and other institutions was calculated by including an interaction term in the model. For all tests, a two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed in SPSS 15.0 for Windows software (SPSS Inc., Chicago, IL, United States).

3. Results

The study comprised the results of all 506 curative-intent pancreatoduodenectomies for adenocarcinoma that were reported in Norway during 1998–2004, including 113 resections (22%) at the study hospital, 221 at the three other medium-volume institutions and 172 at the 21 low-volume institutions. Table 1 shows the distribution of the tumours by cancer origin as reported by the pathologists at different institutions ($p < 0.0001$). Although overall 5-year survival was significantly better at the study hospital, involvement of regional lymph nodes ($p = 0.011$) and resection margins ($p = 0.051$) was more frequently reported at the study hospital compared to the other institutions (Table 2). In addition, pathologists at the study hospital sampled more tissue blocks, evaluated more lymph nodes, reported tumour size more consistently, and included more information about status at individual resection margins (Table 3). While almost all conclusions in the reports from the study hospital (more than 98%) included prognostically important information about small-vessel or perineural involvement, this information was most often not available in the conclusions of histopathologic reports from other hospitals (less than 40%). Coinciding with the introduction of the nomenclature for PanIN lesions,[28] reporting at the study hospital of data on precancerous changes increased from 19% in 1998–2001 to 77% in 2002–2004 ($p < 0.001$). Reporting of data on precancerous changes at other institutions increased from 9.6% in 1998–2001 to 17% in 2002–2004 ($p = 0.036$).

In univariate survival analysis, patients who were reported from the study hospital to have node-free resection, had significantly improved long-term survival compared to those reported to have node-free resection at other institutions (Fig. 2A, $p = 0.0005$). For node-positive resections, there was no such difference (Fig. 2B, $p = 0.63$). The increased relative risk of death for N1 resection versus N0 resection was thus significantly higher ($p = 0.005$) at the study hospital (HR 4.15, 95% confidence interval (CI) 2.46–6.99) compared to at other institutions (HR 1.70, 95% CI 1.36–2.12), irrespective of surgical volume (Fig. 3). Survival was better for patients resected at the study hospital regardless of whether or not there had been found resection margin involvement (Fig. 2C, $p = 0.022$; Fig. 2D, $p = 0.017$). Although resection margins had been reported in more detail at the study hospital (Table 3), the increased risk of death for patients with reported margin-involved resection versus margin-free resection was similar ($p = 0.87$) comparing the study hospital (HR 1.91, 95% CI 1.23–2.95) with the other institutions (HR 1.91, 95% CI 1.52–2.42). Patients reported to have tumour size $\leqslant$2.5 cm had significantly improved survival at the study hospital compared to those in the other institutions (Fig. 2E, $p = 0.042$), while there was no significant difference between institutions for tumours >2.5 cm (Fig. 2F, $p = 0.80$). Finally, although the anatomic site of cancer origin (pancreas, ampulla, distal bile duct or duodenum) was assessed in more detail at the study hospital (Table 3), standardised evaluation and reporting of tumour origin did not discriminate better between prognostically favourable versus unfavourable subgroups of patients (Supplementary Fig. 1).

Multivariable analysis confirmed that regional lymph node involvement, resection margin involvement and large tumour size was independently associated with poor survival (Table 4A). Regional lymph node involvement was associated with an almost four times increased risk of death when assessed at the study hospital (HR 3.70, 95% CI 2.17–6.31, Table 4B), while the increase in the risk of death was only approximately one-and-a-half when assessed at other institutions (HR 1.52, 95% CI 1.19–1.95, Table 4C) ($p = 0.018$). The effect on prognostic estimates of standardising evaluation of resection margin involvement was less pronounced, due to a strong association between lymph node involvement and resection margin involvement, both at the study hospital ($p < 0.001$)

Table 1 – Pancreatoduodenectomies for adenocarcinomas in Norway 1998–2004 (n = 506).

	Institution					
	Study hospital, $n = 113$		Medium volume, $n = 221$		Low volume, $n = 172$	
Tumour origin						
Ampulla	40	(35.4%)	34	(15.4%)	37	(21.5%)
Duodenum	12	(10.6%)	7	(3.2%)	4	(2.3%)
Distal bile duct	9	(8.0%)	21	(9.5%)	18	(10.5%)
Pancreas	52	(46.0%)	159	(71.9%)	113	(65.7%)

$p < 0.0001$, Chi-square test.

Table 2 – Pancreatoduodenectomies for adenocarcinomas in Norway 1998–2004 (n = 506), patient and tumour characteristics.

	Institution			p-Value[a]
	Study hospital	Medium volume	Low volume	
Five-year survival (%)	26%	19%	13%	0.009
Survival, median (years)	1.7	1.3	1.3	
Perioperative death, 30 d	2.7%	5.0%	7.5%	0.150
Gender, % female	49%	44%	44%	0.381
Age at time of surgery, median (years)	67	69	67	0.183
Tumour size, median	2.5	3.0	2.5	0.692
Tumour size, mean	2.9	3.0	3.1	
Regional lymph nodes involved	60%	50%	42%	0.011
Resection margins involved	39%	28%	31%	0.051
Poorly differentiated tumour	30%	29%	31%	0.904
Pancreatic tumour origin (versus ampullary, biliary or duodenal)	46%	72%	66%	<0.001
Pancreatic or biliary tumour origin (versus ampullary or duodenal)	54%	81%	76%	<0.001

a Study hospital versus all other institutions; Chi-square test for categorical variables, Mann–Whitney test for tumour size and age and log-rank test for survival comparisons.

Table 3 – Pancreatoduodenectomies for adenocarcinomas in Norway 1998–2004 (n = 506), details in histopathologic reports.

	Institution			p-Value[a]
	Study hospital	Medium volume	Low volume	
Number of patients per hospital, mean	113	74	8.2	–
Number of hospitals	1	3	21	–
Tissue sampling				
Number of blocks sampled, median	19	12	15	<0.001
Lymph nodes examined, median	9	5	5	<0.001
Missing information about number of blocks sampled	0	0	1	–
Missing information about number of nodes examined	0	10	7	0.018[b]
pTNM-classification stated	100%	40%	31%	<0.001
Cancer origin assessment, details in conclusion of histopathologic report				
Probable cancer origin stated or discussed	97%	80%	85%	<0.001
Tumour infiltration and relation to adjacent structures described	99%	70%	74%	<0.001
Premalignant changes evaluated (adenoma, dysplasia, in situ carcinoma)	48%	11%	15%	<0.001
Histopathologic characteristics specified in conclusion of report				
Histologic type	88%	21%	31%	<0.001
Grade of differentiation	92%	90%	88%	0.323
Vascular infiltration	98%	12%	35%	<0.001
Perineural infiltration	99%	14%	19%	<0.001
Individual margin assessment, details in conclusion of histopathologic report				<0.001
Margins sufficiently specified (pancreatic, bile duct, retroperitoneal)	96%	8.1%	16%	
Margins partially specified (1–2 margins)	2.7%	43%	51%	
Margins not specified	1.8%	48%	34%	
Tumour size reporting				<0.001
Report concludes with an estimation of tumour size	95%	41%	56%	
Tumour size only described by gross examination	2.7%	44%	31%	
Missing information about tumour size	2.7%	15%	13%	

a Chi-square test (categorical variables) or Mann–Whitney test (blocks, nodes) when not otherwise specified.
b Fisher's exact test.

and at other institutions ($p < 0.001$). The hazard ratios for resection margin involvement did not differ significantly between the study hospital (Table 4B) and other institutions (Table 4C) ($p = 0.41$). Similarly, the increased risk of death for tumour size was not significantly different between institutions (Table 4B and C) ($p = 0.19$).

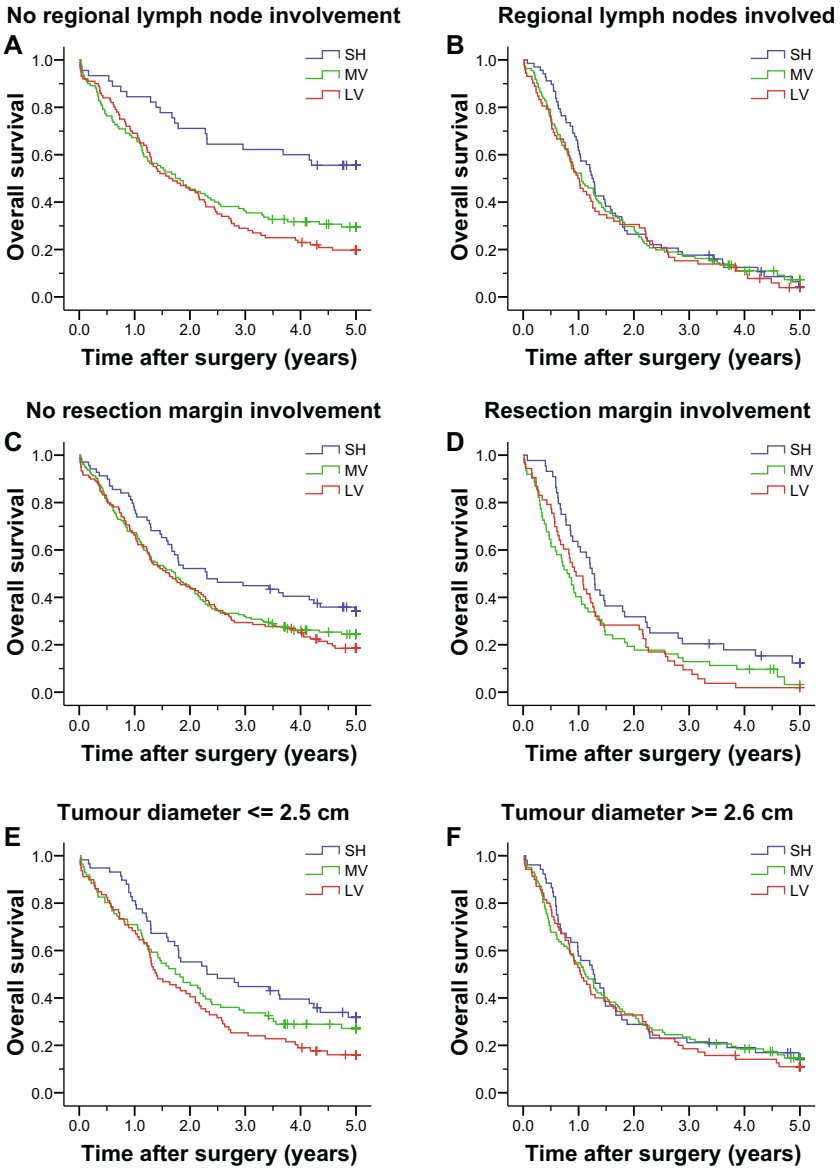

Fig. 2 – Unadjusted survival after pancreatoduodenectomy for adenocarcinoma, by type of institution (SH, study hospital; MV, medium-volume institutions; LV, low-volume institutions), stratified by (A) N0 resections ($n = 255$, $p = 0.00018$), (B) N1 resections ($n = 251$, $p = 0.40$), (C) R0 resections ($n = 347$, $p = 0.022$), (D) R1 resections ($n = 159$, $p = 0.017$), (E) tumour size $\leqslant$2.5 cm ($n = 223$, $p = 0.037$), (F) tumour size >2.5 cm ($n = 224$, $p = 0.61$); log-rank test, SH versus all other institutions.

4. Discussion

This study is the first to compare the direct effect of standardised histopathologic reporting versus non-standardised histopathologic reporting on resected solid tumours using nationwide population-based survival estimates. In pancreatic head adenocarcinomas, studies have shown that identification of prognostic factors such as regional lymph node involvement[17,31] or resection margin involvement[13] significantly improves when histopathologic examination is performed according to a standardised protocol. However, to our knowledge no previous study has compared the effect on survival estimates for each reported histopathologic factor independently, adjusting for the importance of each factor, in a setting of standardised versus non-standardised histopathology reporting.

In Norway, every inhabitant has a unique personal identification number that may be used to link national databases such as the Population Registry and the Cancer Registry, enabling acquisition of nationwide, population-based data on clinical and prognostic factors. The present study, comprising all reported pancreatic head adenocarcinoma resections in Norway in a 7-year period within the last decade, confirms that non-standardised reporting leads to underestimation of regional lymph node[17] and resection margin[13] involvement. In addition, the study demonstrates that non-standardised reporting leads to incomplete reporting for all evaluated histopathologic prognostic factors except degree of differentiation.

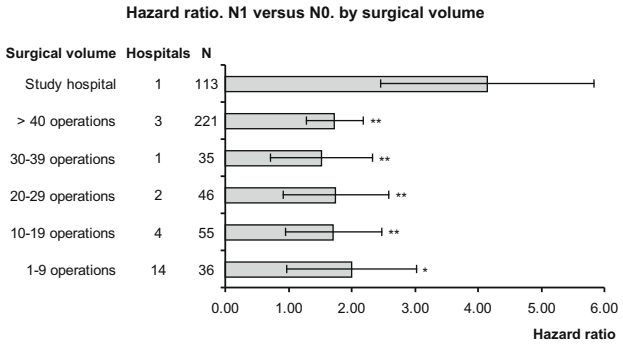

Fig. 3 – Effect of increasing surgical volume on prognostic validity of nodal staging. Hazard ratio >1 indicates unfavourable survival for N1 compared to N0; bars represent hazard ratios with their 95% confidence intervals. $^{**}p < 0.05$ and $^{*}p = 0.142$ for the interactions between hazard ratios for nodal stage versus institutions, comparing institutions of different surgical volumes with the study hospital; Cox regression analysis. N, total number of patients in category.

For example, information about tumour size was more often missing in reports from institutions with non-standardised histopathologic reporting. However, previous studies have demonstrated that tumour size is an independent prognostic factor,[32] which the present study also confirms.

Standardised histopathologic evaluation at the study hospital included the use of a systematic protocol for (a) gross examination, (b) specimen dissection, (c) tissue sampling, (d) microscopic evaluation and in addition (e) the use of a template for histopathologic reporting. A possible limitation of the study is that we did not collect information from the other institutions about the first four steps (a–d). All five steps are important for consistency and completeness of reporting. For the pathologist, template reporting serves as a checklist, ensuring that examination was in fact performed according to the protocol. For the clinician, template reporting provides a clear, concise and consistent report on the key histopathologic findings, which the clinician may need in order to decide on adjuvant treatment options or enrollment in clinical trials. Template reporting also facilitates changes of practice at

Table 4 – Pancreatoduodenectomies for adenocarcinomas in Norway 1998–2004, multivariable survival analysis of 447 cases[a].

	Percent of resections (%)	Hazard ratio	95% CI for hazard ratio	*p*-Value
A. Overall analysis ($n = 447$)[a]				
Type of institution				
Study hospital	25	1 (ref)		0.005
Medium-volume institutions	42	1.39	1.06–1.83	0.018
Low-volume institutions	33	1.59	1.20–2.10	0.001
Regional lymph node involvement				
N0	51	1 (ref)		
N1	49	1.80	1.44–2.25	<0.001
Resection margin involvement				
R0	68	1 (ref)		
R1	32	1.78	1.42–2.24	<0.001
Tumour size, best estimation of maximum diameter[b]				
⩽2.0 cm	31	1 (ref)		0.002
2.1–3.0 cm	34	1.47	1.12–1.92	0.005
>3.0 cm	35	1.58	1.21–2.06	0.001
Age, years				
<60	29	1 (ref)		0.017
60–74	52	1.28	1.00–1.64	0.049
>75	19	1.55	1.14–2.10	0.005
Gender				
Female	55	1 (ref)		
Male	45	0.99	0.80–1.22	0.915
B. Study hospital ($n = 110$)[a]				
Regional lymph nodes involved, N1 versus N0	62	3.70	2.17–6.31	<0.001
Resection margins involved, R1 versus R0	40	1.41	0.90–2.23	0.137
Increasing tumour size, >2.5 cm versus ⩽2.5 cm	47	1.90	1.23–2.95	0.004
Increasing age, >65 years versus ⩽65 years	54	1.41	0.91–2.19	0.122
Gender, male versus female	51	0.94	0.61–1.46	0.785
C. Other institutions ($n = 337$)[a]				
Regional lymph nodes involved, N1 versus N0	45	1.52	1.19–1.95	<0.001
Resection margins involved, R1 versus R0	30	1.94	1.49–2.52	<0.001
Increasing tumour size, >2.5 cm versus ⩽2.5 cm	51	1.23	0.97–1.57	0.092
Increasing age, >65 years versus ⩽65 years	60	1.26	0.98–1.61	0.067
Gender, male versus female	56	1.01	0.80–1.29	0.925

a Tumour size not reported in 3 (study hospital) and 56 (other institutions) cases (thus 59 of 506 cases excluded from multivariable analysis).
b Diameter as reported in the concluding, microscopic or macroscopic sections of the report (in this order).

pathology institutions, for example with respect to updates on TNM-classification or reporting of precancerous lesions. Thus, after the new nomenclature for PanIN lesions had been proposed in 2001[28] and subsequently included in the template at the study hospital, information about possible precancerous changes was reported four times more often at the study hospital while only twice as often at other institutions.

The direct effect on survival estimates of standardising histopathologic reporting was evaluated by comparing the survival estimates based on the histopathologic reports from the different types of institution. The study confirms that increasing hospital volume is associated with reduced perioperative mortality and improved long-term survival (Table 2).[33,34] However, standardised reporting may matter more than institutional volume for accuracy of long-term survival estimates. While medium- and low-volume institutions generally reported with the same level of detail, there were prominent differences in reporting (Table 3) and univariate survival (Figs. 2 and 3) when comparing the study hospital and medium-volume institutions. In particular, the relative risk of death for patients with lymph node involvement versus patients with no lymph node involvement was significantly higher at the study hospital compared to other institutions (Fig. 3 and Table 4B and C). Standardised reporting for lymph node involvement seems to be more important for accuracy of survival estimates than standardised reporting for resection margin involvement, tumour size and cancer origin. Not only R0 resected patients but also R1 resected patients had a better prognosis at the study hospital compared to the other institutions. There was a significant association between resection margin and lymph node involvement. In addition, resection margin involvement was more frequently detected at the study hospital, and stage migration could thus also explain why the prognosis was better for both the subgroups.

Standardising the evaluation of cancer origin (pancreatic, biliary, ampullary or duodenal) did not discriminate better between prognostically favourable (ampullary and duodenal) and unfavourable (pancreatic and biliary) subgroups of resected pancreatic head adenocarcinomas (Supplementary Fig. 1). Standardising the histopathologic assessment is the most probable explanation for the higher proportion of ampullary (and duodenal) tumours at the study hospital (Table 1), in accordance with the data published by Verbeke and colleagues.[13] Although the overall analysis showed significantly better survival at the study hospital than at the other institutions (Table 2), there were no differences stratifying by tumour origin (Supplementary Fig. 1). Non-standardised evaluation could result in misdiagnosis with respect to tumour origin, possibly skewing the prognostic estimates for pancreatic tumours in a positive direction.[24] Furthermore, the histologic type, which is typically either pancreatobiliary or intestinal,[23] might have been taken into consideration by pathologists at the institutions other than the study hospital when determining the tumour origin. In WHO classification of gastrointestinal tumours, the tumour origin (topographic diagnosis) and the histologic type (morphologic phenotype) are two distinct features.[35] In the present study, reports from institutions other than the study hospital very seldom concluded with a histologic type other than the typical ductal pancreatic adenocarcinoma. Histologic variants of ductal pancreatic adenocarcinoma have in fact been increasingly acknowledged in recent years, and these are of importance since these variants have distinct clinical and pathological features.[36–38] Some ductal adenocarcinomas of pancreatic[23,38,39] and biliary origin[23,40,41] may in fact be intestinally differentiated, although most are pancreatobiliary. Both these histologic types are frequently found among ampullary adenocarcinomas,[19,23,42] of which the pancreatobiliary type has the poorest prognosis.[19,21,23,42–44]

In two recent reports,[23,45] we compared tumour origin and histologic type (pancreatobiliary versus intestinal) and demonstrated that overall survival after curative-intent pancreatoduodenectomy depended more on the histologic type than on the assumed anatomic cancer origin. In resections for pancreatobiliary-type adenocarcinomas of comparable size, the tumour origin (ampulla, distal bile duct or pancreas) was not significantly associated with the prognosis. The histologic type is thus a better prognostic indicator than the anatomic tumour origin and is also easier to determine. Conclusive identification of the tumour origin in pancreatic head adenocarcinomas may in certain cases be impossible, in particular when the tumour involves more than one of the sites of potential origin.[7,14,18–21,46] Incorrect cancer origin classification also has implications for TNM-classification since criteria are different for the different origins.[9,47] Furthermore, many patients in fact lack a defined ampulla,[48] and the need for a separate TNM-classification for ampullary adenocarcinomas may indeed be questioned.[22,49]

Knowledge about molecular pathways involved in cancer development and progression is rapidly increasing. In order to evaluate the effect of new treatments, a first step should be to ascertain that inclusion and stratification in clinical trials is adequate. Many previous trials, for instance the ESPAC-1[50] and CONKO-001[16] studies, have often been performed without sufficient standardisation and quality control on histopathology. The lack of standardisation might cast doubt on some of the results and conclusions drawn from such studies. The present study demonstrates, using population-based nationwide data on resected pancreatic head adenocarcinomas, that standardisation of histopathologic reporting significantly improves diagnostic accuracy and prognostic estimates. In particular, standardised histopathologic reporting was crucial for adequate lymph node evaluation. To evaluate clinical trials on resected solid cancers, standardised histopathologic reporting should be mandatory.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2009.03.019.

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