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Intra-observer Agreements in Multidisciplinary Team Assessments of Pancreatic Cancer Patients

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Running head:

Variance in Pancreatic Cancer Treatment.

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Synopsis:

Variations in pancreatic cancer treatment between different centers have been shown. In the present study, we observed a substantial variation even within each center.

ABSTRACT

Background and Methods:

Treatment strategies for pancreatic cancer patients are made by a multidisciplinary team (MDT) board. We aimed to assess intra-observer variance at MDT boards. Participating units staged, assessed resectability, and made treatment allocations for the same patients as they did two years earlier. We disseminated clinical information and CT images of pancreatic cancer patients judged by one MDT board to have non-metastatic pancreatic cancer to the participating units. All units were asked to re-assess the TNM stage, resectability, and treatment allocation for each patient. To assess intra-observer variance, we computed %-agreements for each participating unit, defined as low (<50%), moderate (50-75%), and high (>75%) agreement.

Results:

Eighteen patients were re-assessed by six MDT boards. The overall agreement was moderate for TNM-stage (50%-70%) and resectability assessment (53%) but low for treatment allocation (46%). Agreement on resectability assessments were low to moderate. Findings were similar but more pronounced for treatment allocation. We observed a shift in treatment strategy towards an increasing neoadjuvant chemotherapy, particularly in patients with borderline resectable and locally advanced cancers.

Conclusions:

We found substantial intra-observer agreement variations across six different MDT boards of 18 pancreatic cancer patients with two years between the first and second assessment.

Keywords: pancreatic cancer, resectability, treatment allocation, variation, neoadjuvant chemotherapy.

INTRODUCTION

Pancreatic cancer is the fourth-leading cause of cancer-related death in the western world [1]. It is associated with a dismal prognosis; only 10% survive beyond five years from diagnosis [2]. Curative-intent surgery is the only chance for long-term survival, but only 20% of patients are eligible for surgical treatment, as most patients present with locally advanced or metastatic disease [3,4].

The treatment strategy for pancreatic cancer patients is usually made by a multidisciplinary team (MDT) board, where surgeons, radiologists, oncologists, and other relevant medical professionals design a treatment plan tailored each patient. MDT conferences are widely adopted to ensure that patients with cancer receive optimal treatment and to mitigate variations in treatment [5].

Although well-defined criteria for classification of pancreatic cancer resectability are available [6–9], substantial variations in pancreatic cancer assessments by the MDT boards have been shown [10–12]. In a previous study, we examined the agreements in the evaluation of pancreatic cancer patients performed at seven different MDT boards [10]. While we observed some agreement in TNM-staging, there were substantial disagreements in resectability assessments and treatment allocations. Other studies have shown that evaluation at MDT boards changed the proposed treatment strategy in up to 25% of patients with pancreatic cancer [11,12]. Some of this disagreement may be due to differences in local traditions, but treatment allocations may also depend on the individual participants represented at the MDT board.

In addition to variation in pancreatic cancer treatment between the units, there may also be variation within each unit (intra-observer variance). In the present study, we aimed to examine intra-observer variance at MDT boards and changes in treatment strategies over time. Thus, the participating units evaluated the same imaging material as

they did approximately two years earlier for TNM-staging, resectability assessment, and treatment allocation. We then compared the first and second evaluation within each participating unit.

MATERIALS AND METHODS

Setting

In 2019, we published the first study of MDT assessments of pancreatic cancer patients including seven international participating centres [10]. Here, we conducted a follow-up study among six of the seven units (Odense University Hospital, Denmark; Stavanger University Hospital, Norway; Sahlgrenska University Hospital, Sweden; Maastricht University Medical Centre, The Netherlands; University Medical Centre Groningen, The Netherlands; and the Royal Infirmary of Edinburgh, United Kingdom). One of the seven units in the first study declined to participate. All units are located within tax-financed universal healthcare settings with no competing private institutions for surgical treatment of patients with pancreatic cancer.

Study design and population

The study design has previously been described in detail [10]. In brief, 20 patients with CT-assessed pancreatic cancer without apparent signs of distant metastases were randomly selected for evaluation by the participating MDT boards. One patient (patient ID 5) with metastatic lesions was accidentally included and subsequently excluded from the study. Because of technical issues at one unit in the first evaluation, one patient (patient ID 17) was also excluded from analyses to ensure anonymity among the participating units. Thus, in the present study, 18 out of 19 patients evaluated in the first study were re-assessed by the MDT boards approximately two years after the initial assessment.

Evaluation at the MDT boards

As in the first study, all patients were reviewed by the MDT boards based on the anonymized CT imaging material and patient information disseminated (Appendix 1). No other information was available to the participating MDT boards. The MDT boards were asked to evaluate the TNM stage, according to the seventh edition of the AJCC classification (which was used in the first study) [13], assess resectability (judged by the MDT board) as resectable, borderline resectable, not resectable - locally advanced disease, not resectable - metastatic disease, or unable to decide, and to suggest a treatment allocation (resection; further investigation; neoadjuvant chemotherapy; palliative chemotherapy; best supportive care; other) for each patient. Data were entered into REDCap [14]. The cancers were staged according to the AJCC classification with some modifications. We allowed the use of Nx and Mx categories if participants were unable to assess nodal status or presence of metastases based on the available material. To mitigate the impact of missing data, records with missing values were manually assessed and replaced with an appropriate value based on the participants' comments. All data replacements are documented in Appendix 2-3 and approved by the respective units.

Composition of the MDT boards

At all participating institutions, the MDT boards consisted of surgeons, radiologists, and medical oncologists. Pathologists and medical gastroenterologists were represented at the MDT boards in five of the institutions. At two institutions, physicians specialized in nuclear medicine participated in the MDT meeting.

Statistical analysis

For each unit, we computed the %-agreement for TNM-stage, resectability assessment, and treatment allocation using the first evaluation as the reference standard. For each

estimate, we also calculated the associated 95% confidence interval (CI), with the lower confidence limit truncated at zero. We defined agreement as identical values in the first and second evaluation, and %-agreement as low (<50%), moderate (50-75%), and high (>75%). Values of Tx, Nx, or Mx and 'unable to decide' for resectability assessment were considered as distinct values. Continuous variables are presented as median with interquartile range (IQR) and categorical variables as numbers and percentages. All statistical analyses were performed using Stata version 15 (StataCorp, College Station, Texas, USA).

Ethical considerations

This study, including the dissemination of information on anonymized patients, was approved by the Danish Data Protection Agency (*j.no.* 1-16-02-831-17). According to Danish law, ethical approval was not required.

RESULTS

Study population

For this study, we included 18 patients considered by the MDT board at Aarhus University Hospital to have non-metastatic pancreatic cancer. Median age at diagnosis was 67 years, and two-thirds were men. Clinical characteristics including information on tobacco smoking and alcohol consumption, performance status, and blood samples are presented in the first study [10].

Intra-observer agreement for TNM-stage, resectability assessment, and treatment allocation

There were some variations in intra-observer agreement for TNM-staging of the 18 included patients (Table 1 and Figure 1). Overall, %-agreements were lowest for T-stage and highest for M-stage (Figure 1). Two units had >50% agreement on T-stage (78% and

61%, respectively), whereas four units had >50% agreement on N-stage. Four units had a high agreement on M-stage, whereas two units had a low agreement. For each unit, the number of agreements and disagreements for each variable is outlined in Figure 2A-C. A detailed overview for each unit and patient is available in Appendix 4-9.

Overall, the %-agreement on resectability assessments was 53% (95% CI: 43%-62%), Table 1 and Figure 1. Two units had a low agreement and four units had a moderate agreement on resectability assessment. The findings were more pronounced for treatment allocation (Table 1 and Figure 1). Half of the units had a low agreement and half had a moderate (56%, 50%, and 61%) agreement on treatment allocation. For each unit, the number of agreements and disagreements for each variable is outlined in Figure 2D-E. A detailed overview for each unit and patient is available in Appendix 4-9.

Changes in treatment strategy over time

We observed that, during the two years that elapsed between the first and second evaluation, the participating units became increasingly inclined to use neoadjuvant chemotherapy (Table 2 and Figure 3). This was particularly evident in patients considered to have borderline resectable tumors, in which we observed a shift in treatment strategy from upfront resection/further investigation to neoadjuvant chemotherapy. This was also evident in patients with locally advanced tumors, in which treatment shifted from palliative chemotherapy to neoadjuvant chemotherapy (Figure 4). Still, there were substantial inter-unit variations in the use of neoadjuvant chemotherapy (Table 2). In one unit, the use increased from 6% to 28%. Three units allocated patients to neoadjuvant chemotherapy in the second but not in the first evaluation. One unit did not allocate patients to neoadjuvant chemotherapy at all.

DISCUSSION

In the present study, we showed a substantial intra-observer variance at MDT boards on assessments of TNM-stage, resectability, and treatment plans in pancreatic cancer patients. Moreover, we demonstrated an intriguing change in treatment strategies, as several units became more inclined to use neoadjuvant chemotherapy in borderline resectable and locally advanced pancreatic cancers.

The observed variance in pancreatic cancer assessments within the same MDT boards underlines that this remains a very challenging task, and reasons for the disagreements are likely multifactorial. TNM-stage is a fixed, objective variable, and we used the same staging system in both the first and second evaluation. All CT scans were reviewed by same 1-2 radiologists at each center (who also reviewed the scans in the first study), except for one center (Unit 6) who had up to five different radiologists. The agreement in TNM-staging was not lower for this center than for the remaining participants. Intra-observer variance between the radiologists is therefore not a likely explanation for variations in TNM-staging. Instead, this could potentially be explained by imprecise evaluation of the imaging material or by random variation. In contrast, resectability criteria are possibly more likely to be prone to different interpretations by individual doctors. Despite the availability of resectability classification systems in pancreatic cancer [6–9], we have previously shown that the adherence to such classifications may differ between units [10], underlining that the definition of borderline resectable pancreatic cancer is, at least partly, subjective. Another, more optimistic, explanation may be that the individual units have improved their treatment of pancreatic cancer patients during the past years. This would contribute to the intra-observer disagreements over time, as more patients are possibly now more correctly staged than two years ago. Finally, changes in the composition of the different MDT boards, which

could alter group dynamics and facilitate disagreement owing to the participating doctors' personal preferences, could theoretically affect the results. However, in the period between the first and the present study, none of the centers had any change in key personnel on the MDT boards. In addition, all members of the MDT boards were senior physicians with at least five years of clinical experience with pancreatic cancer patients. Naturally, younger doctors participated in the MDT meetings, but they were always conducted with consulting pancreatic surgeon and radiologists present. A learning-curve effect is therefore unlikely.

The increasing use of neoadjuvant chemotherapy demonstrated in this study, particularly in patients with borderline resectable and locally advanced cancers, is notable. During the study period, three centers participated in ongoing trials on neoadjuvant chemotherapy. This also materialized in the findings of our study, as these three centers were more prone to consider neoadjuvant chemotherapy compared with their first evaluation. Whereas the survival benefit in adjuvant chemotherapy is well documented [15], there is more controversy regarding neoadjuvant chemotherapy [16]. The recently published Dutch PREOPANC trial of 248 patients with resectable or borderline resectable pancreatic cancer found that treatment with neoadjuvant chemoradiotherapy seemed to increase both resection and R0 rate but with no survival benefits [17]. However, in the subgroup of patients with borderline resectable cancers, neoadjuvant treatment improved median overall survival from 13 to 17 months [17]. In summary, neoadjuvant oncological therapy may increase survival in selected subgroups. Therefore, the increasing use of such regimens, as demonstrated in the present study, could potentially contribute to improved survival rates in pancreatic cancer.

Some limitations of our study should be noted. First, for logistical reasons, our study population was limited. Thus, estimates of %-agreements had somewhat limited precision, and should therefore be cautiously interpreted. Second, it is unknown if the two-year washout period from the first to the second evaluation is sufficient to minimize the risk of the radiologists remembering the first evaluation. However, radiologists see a substantial amount of patient's imaging during two years, so this is of limited concern. Third, as pointed out in our first study on this topic [10], the MDT settings within this study are somewhat artificial. The units are aware that the imaging material is not from their own institution, which could impair the external validity. However, the participating units were asked to conduct the second evaluation in the same manner as the first evaluation, limiting this concern. Fourth, we chose to compute %-agreement, as this is a simple measure that can be used with any measurement scale. However, it does not account for agreement occurring by chance. This could potentially overestimate the true agreement, specifically for variables with few treatment options (N- and M-stage).

Our study has some important clinical implications, demonstrating that pancreatic cancer assessments remain an incredibly challenging and highly specialized job. In Denmark, weekly national virtual MDT conferences with participation of all centres performing pancreatic cancer surgery are implemented. Here, all patients with non-metastatic non-resectable pancreatic cancer are assessed in order to select the best treatment strategy. However, the outcome of this conference has not yet been examined. The increasing use of neoadjuvant chemotherapy shown in this study is exciting and could improve survival rates from pancreatic cancer. Still, it remains unknown, whether assessments of pancreatic cancer patients by MDT boards infer any survival improvements.

CONCLUSIONS

In conclusion, we found substantial intra-observer agreement variations in six different Northern European MDT boards of the same 18 pancreatic cancer patients with two years between the first and second assessment. This is likely multifactorial, but part of the disagreement is explained by an increasing use of neoadjuvant chemotherapy.

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Anonymized patient-level data is available in the Appendix. Analytical code can be provided upon request. This study was not preregistered in an institutional registry. No conflicts of interest are present.

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FIGURE LEGENDS

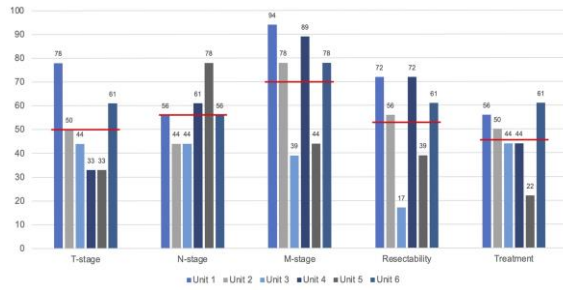


Figure 1. %-agreement for each unit for TNM-stage, resectability assessment, and treatment allocation (red line: overall %-agreement), using the first evaluation as the reference standard.

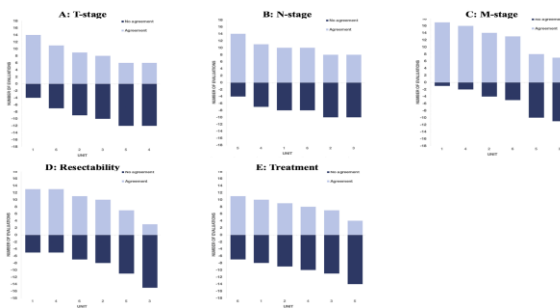


Figure 2. Number of agreements and disagreements for each unit for TNM-stage, resectability assessment, and treatment allocation.

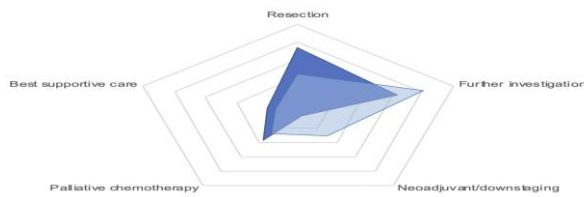


Figure 3. Overall change in treatment strategies between first and second evaluation (dark blue: first evaluation; light blue: second evaluation).

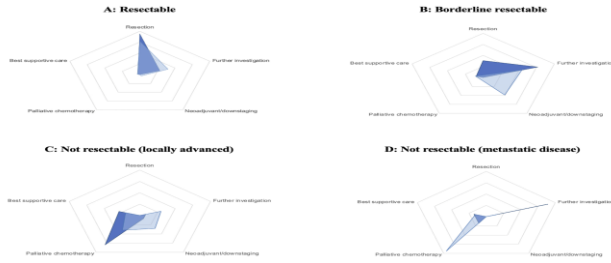


Figure 4. Change in treatment strategies between first and second evaluation for each resectability assessment (dark blue: first evaluation; light blue: second evaluation).

Table 1. %-agreement for each unit for TNM-stage, resectability assessment, and treatment allocation (95% CI), using the first evaluation as the reference standard.

	Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Unit 6
T-stage	78%	50%	44%			61%
	(57%- 99%)	(24%- 76%)	(19%- 70%)	33% (9%- 57%)	33% (9%- 57%)	(36%- 86%)
N-stage	56%	44%	44%	61%	78%	56%
	(30%- 81%)	(19%- 70%)	(19%- 70%)	(36%- 86%)	(57%- 99%)	(30%- 81%)
M-stage	94%	78%	39%	89%	44%	78%
	(83%- 100%)	(57%- 99%)	(14%- 64%)	(73%- 100%)	(19%- 70%)	(57%- 99%)
Resectability	72%	56%		72%	39%	61%
	(49%- 95%)	(30%- 81%)	17% (0%- 36%)	(49%- 95%)	(14%- 64%)	(36%- 86%)

Treatment	56%	50%	44%	44%		61%
	(30%-	(24%-	(19%-	(19%-	22% (1%-	(36%-
	81%)	76%)	70%)	70%)	43%)	86%)

Table 2. Treatment strategy for each unit, comparing first and second evaluation.

	Unit 1		Unit 2		Unit 3		Unit 4		Unit 5		Unit 6	
	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd
Resection	56	56	39	28	22		22	17	56		28	22
	%	%	%	%	%	6%	%	%	%	6%	%	%
Further investigation	17	17	28	33	28	44	50	44	28	44	44	61
	%	%	%	%	%	%	%	%	%	%	%	%
Neoadjuvant/down staging		28		22				17		22		
	6%	%	0%	%	0%	0%	0%	%	6%	%	0%	6%
Palliative chemotherapy	11		17		33	39	17	11		22	28	11
	%	0%	%	0%	%	%	%	%	6%	%	%	%
Best supportive care	11		17	17	17	11	11	11				
	%	0%	%	%	%	%	%	%	6%	6%	0%	0%