Acta Oncologica, 2016; 55: 265–277

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ORIGINAL ARTICLE

Impact of early disease progression and surgical complications on adjuvant chemotherapy completion rates and survival in patients undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma – A population-based cohort study

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ABSTRACT

Background. Multimodality treatment (MMT) improves survival for patients with pancreatic ductal adenocarcinoma (PDAC). The surgery-first (SF) strategy is the most universally accepted approach.

Material and methods. Population-based retrospective cohort study of all cases of resectable PDAC from 2006 to 2012. Patients were planned for adjuvant chemotherapy (AC) with the Nordic 5-fluorouracil/leucovorin regimen. Reasons for and rates of failure to complete AC, postoperative major complications (PMC), and overall survival (OS) were analysed.

Results. Of 203 patients, 85 (41.9%) completed AC, 41 (20.2%) failed to complete AC, and 77 (37.9%) never initiated AC. Primary reasons for not initiating or completing AC were early disease progression (34.7%), postoperative complications/poor performance status (32.2%), and age > 75 years (24.6%). Median OS in the whole cohort was 17.0 months, and 20.0 months in patients who initiated AC. Median OS in patients who completed AC was higher than in patients who did not (25.0 months vs. 12.0 months, $p < 0.001$). PMC ($n = 41$) were associated with decreased initiation rate ($p < 0.001$) and completion rate ($p = 0.007$) of AC, and decreased median OS (11.0 months vs. 19.0 months, $p = 0.028$). Among patients with R1 resection, PMC again were associated with worse median OS (8.0 months vs. 16.0 months, $p = 0.028$). Multivariate analysis demonstrated that completion of MMT and tumour grade (G1/G2) were related to mortality rate ($p < 0.001$). Mortality risk for patients who completed AC was reduced also when adjusting for competing risk (SHR 0.426, $p < 0.001$).

Conclusions. MMT completion is strongly associated with reduced mortality risk in patients with resectable PDAC undergoing the SF approach. Early disease progression and PMC/poor performance status preclude MMT completion in more than one third of the patients. These reasons for failure to complete MMT underscore the need for strategies to improve patient selection and reduce surgical morbidity in patients with resectable PDAC.

Pancreatic cancer is the fourth leading cause of cancer-related deaths in Europe and the US [1]. While surgical resection remains the foundation for potentially curative treatment, it alone rarely provides long-term survival [2]. Thus completion of multimodality treatment (MMT) is the ideal goal and standard of care for treatment of pancreatic ductal adenocarcinoma (PDAC) [2,3]. Surgical

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(Received 31 January 2015; accepted 24 June 2015)

ISSN 0284-186X print/ISSN 1651-226X online © 2015 Informa Healthcare
DOI: 10.3109/0284186X.2015.1068445

intervention for PDAC has a high perioperative morbidity rate of 40–60% and a perioperative mortality rate of 2–4% [4,5]. Furthermore, a significant proportion of patients have early disease progression within months after resection [6,7]. However, clinicians cannot yet accurately predict which patients will experience early distant spread of disease.

In treating pancreatic cancer, there is no clearly defined optimal sequence of surgery, chemotherapy, and radiation therapy. The surgery-first (SF) strategy is the most universally accepted evidence-based approach to resectable PDAC [8]. However, some centres advocate the neoadjuvant therapy (NT) sequencing strategy as an alternative to the SF approach [9]. Proponents of SF sequencing argue that NT strategies may preclude from surgery up to 25% of patients initially thought to be radiographically resectable. These patients fail to receive resection after NT due to early manifestation of metastases, inability to optimise performance status or comorbidities during NT, and very rarely local progression alone [9]. There remains no prospective evidence of an advantage of one sequencing strategy over the other. There are several ongoing randomised studies on NT versus the SF approach. The only published randomised study so far is on neoadjuvant chemoradiotherapy versus SF [10]. However, the results were not significant and the study was terminated early due to slow recruiting.

Adjuvant chemotherapy (AC) has a significant survival benefit in patients with resected PDAC [2,11]. Accordingly, the use of AC has increased during the last 15 years [12–14]. It is known that completion of AC can be precluded by early cancer progression and by treatment complications [7,15]. The primary aim of this study was to examine the impact of early disease progression and surgical complications on AC completion rates and survival in patients treated with a SF sequencing strategy for resectable PDAC.

Material and methods

Patients

The South-Eastern Norway Regional Health Authority is comprised of 10 hospital trusts with a well defined geographic population comprising approximately 2.8 million people or 56% of the population of Norway. The study hospital is the only tertiary referral hospital for Hepato-Pancreato-Biliary (HPB) surgery in South-Eastern Norway, and performs pancreatic resections of all cases of PDAC in this region. From January 2006 to December 2012, 215 consecutive patients with PDAC underwent surgical resection with curative intent. Patients with R2 resections (n = 4) or distant metastasis at the time of resection (n = 3) were excluded from further analysis. Patients who had undergone preoperative radiochemotherapy (n = 5) were also excluded. Patient data were retrieved prospectively from the institutional pancreatic database and retrospectively from hospital records. Final date of data collection was 31 December 2013. The study was approved by the institutional Data Protection Officer for Research. The study was initiated and designed during an observership period (authors KJL, BAB) at MD Anderson Cancer Center (MDACC) (authors MHK, CWT) in June 2013 as part of the Global Academic Program (GAP) of MDACC. GAP facilitates and administers MDACC's Sister Institution Network and the connection between MDACC and the Norwegian Cancer Consortium.

During the study period 2006–2012 a total of 2648 cases (1303 male, 1345 female) of pancreatic cancer were diagnosed in the region of South Eastern Norway (NORDCAN database, http://www-dep.iarc.fr/NORDCAN/english/frame.asp). The cancer site dictionary used in NORDCAN is based on the International Classification of Disease and is given by codes used in the 10th revision (ICD-10). For pancreatic cancer the ICD-10 code is C25 including all malignant tumours of the pancreas (also endocrine). Patients with other histological variants of pancreatic cancer (n = 152) were not included in the present study (pancreatic neuroendocrine tumour n = 88, intraductal papillary mucinous neoplasia n = 39, solid pseudopapillary neoplasm n = 13, mucinous cystadenocarcinoma n = 3, acinar cell carcinoma n = 2, adenosquamos carcinoma n = 2, undifferentiated carcinoma n = 2, pancreatic neuroendocrine carcinoma n = 2, anaplastic carcinoma n = 1). Accordingly the resection rate for malignant pancreatic tumours in South-Eastern Norway in the study period was 13.9% (367/2648).

Staging and data definitions

All patients had radiographically resectable pancreatic tumours and performance status and comorbidities suitable for immediate surgery. Vascular resection and reconstruction of the portal vein (PV) or superior mesenteric vein (SMV) have been performed on a routine basis in our hospital from 2006 with standard indications (no tumour extension to the superior mesenteric artery or celiac axis, no occlusion of the PV or SMV, PV or SMV encasement $< 180°$). Patients with "short-segment" encasement of the common hepatic artery or the proper hepatic artery, typically at the gastroduodenal artery origin, were resected in highly selected cases. Data were analysed for clinical, pathological, and treatment factors. Preoperative workup included

multidetector computed tomography (CT) with a standard protocol optimised for imaging pancreatic tumours, and chest CT within one month prior to surgery. Until 2007 the pathologist reported a margin positive (R1) only if tumour cells were present at the surface (clearance equals 0 mm). From 2008 the definition was consistently changed to a 1 mm clearance [16]. Measurement of serum CA 19-9 was not mandatory prior to surgery.

Multimodality therapy, postoperative major complications, and surveillance

Adjuvant fluorouracil (500 mg/m^2) and leucovorin (60 mg/m$^{2)}$ was administered Day 1 and 2 every second week for six months (12 cycles), and recommended to patients $\leq$ 75 years old, ECOG 0-1, and scheduled within eight weeks of operation [11,17,18]. Postoperative major complications (PMC) were defined as Clavien Grade $\geq$ 3 [19]. Perioperative death was defined as death within 30 days of operation or in-hospital death. Reasons for and rates of failure to complete AC, 90-day PMC, and OS were analysed. Patients were followed regularly with history and physical examination to identify postoperative complications and symptoms. Abdominal and chest CT were performed six months after surgery or if the patients had symptoms, signs or increased CA 19-9 values suspicious for recurrence. Disease progression was considered early when it was documented by CT during the period of AC within five months of surgery. After six months, the follow-up was tailored to each patient's clinical scenario. Follow-up data was complete in all patients, and no patients were lost to follow-up. Localisation of recurrence was based on CT findings except in three patients where it was based on symptoms, clinical findings or abdominal ultrasound. Recurrence was defined as radiological evidence of intra-abdominal soft tissue around the surgical site or of distant metastasis. Patients with recurrence were referred for palliative chemotherapy or radiotherapy with or without concurrent capecitabine, and to the Palliative Care Unit for assessment of symptoms and to receive the best palliation of symptoms. Overall survival (OS) data were obtained from the National Population Registry in Norway.

Statistical methods

Data were described with median and range (continuous variables) and with counts (categorical variables). Crude patient-, tumour-, and treatment characteristics were compared between patients receiving complete AC and patients receiving no or incomplete AC using the Mann-Whitney test for continuous variables and the χ^2-test for categorical variables (in case of small numbers, Fisher's exact test was used). The impact of resection margins and lymph node status on OS in patients with and without PMC were analysed using non-parametric tests. Crude OS and median survival were estimated using the Kaplan-Meier method and compared between patients groups using the log-rank test. Survival was defined as time from surgery to death of any cause or the end of follow-up through 31 December 2013 whichever came first.

Cox regression analyses were used to assess the prognostic capacity of patient, tumour and treatment characteristics on mortality risk. Continuous variables, such as age, tumour size and lymph node ratio, were categorised as follows: age $\leq$ or $>$70 years, tumour size $\leq$ or $>$2.0 cm, and lymph node ratio $\leq$ or $>$0.2. All clinipathological relevant prognostic variables associated with mortality risk from univariate regressions were entered into a multivariate model. As nodal status and lymph node ratio were highly associated, only lymph node ratio was entered into the final multivariate model. Backward stepwise multivariate approach was used to identify independent prognostic factors. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). In total, the number of events in our dataset was 162. However, we did not have information regarding lymph node status/lymph node ratio in three patients. Therefore, for multivariate analysis the number of events was 159.

Some patients never completed AC and some patients were never offered AC. When comparing OS, patients who completed AC have an obvious survival gain of six months, which is the length of AC treatment. Moreover, we had the date of discontinuation of AC available. Therefore we were able to compute time to discontinuation of AC. To correct for the competing event of discontinuation of AC, we have modelled both the cumulative mortality and mortality risk with competing risk approach (Fine and Grey). The main event was death of any cause and the competing event was not completing AC. The results are presented as plots with cumulative incidences and the difference in mortality rates is summarised as sub-hazard ratio (SHR) with 95% CI.

All tests were two-sided, and p-values $<$ 0.05 were considered statistically significant. Statistical analyses were performed in SigmaPlot 9.0 for Windows (Systat Software, San Jose, CA, USA) and SPSS 19 for Windows (SPSS, Inc., Chicago, IL, USA). Competing risk regression analysis was performed in STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

Patient characteristics and operations

Patient, tumour and treatment characteristics are presented in Table I. A total of 203 patients (95 women

and 108 men) met inclusion criteria and underwent an R0/R1 surgical resection for PDAC. Median age at surgery was 67 (range 34–84) years. The procedures performed included pylorus-preserving pancreatoduodenectomy (n = 115), pancreatoduodenectomy with antrectomy (n = 52), distal pancreatectomy with splenectomy (laparotomy n = 3, laparoscopic n = 23), and total pancreatectomy with splenectomy (n = 10). Vascular resection and reconstruction was performed in 38 patients (18.7%), consisting of PV and SMV resection in 35 patients, combined PV/SMV and hepatic artery resection in two patients, and resection of the hepatic artery in one patient. PV and SMV reconstruction was accomplished through partial resection in 17 patients (transverse suture n = 9, patch closure n = 8) and segmental resection in 20 patients (primary end-to-end anastomosis n = 10, interposition grafting n = 10). Arterial reconstruction was accomplished through re-implantation of the right hepatic artery to the proper hepatic artery in two patients, and interposition grafting of the proper hepatic artery in one patient. Preoperative serum CA 19-9 levels was available in 92 patients (45.3%).

Postoperative complications

Perioperative mortality was 2.5% (5/203). Perioperative morbidity (all grades) was 53.2% (108/203). PMC (Clavien Grade ≥ 3) were experienced in 41 patients (20.2%).

Adjuvant chemotherapy

Reasons for and rates of failure to complete AC are given in Figure 1. Of the 126 (62.1%) patients who initiated AC, 85 completed it and 41 did not. In 77 (37.9%) patients AC was never initiated. All patients received fluorouracil and leucovorin except 10 patients who received gemcitabine. The median number of cycles received in patients who initiated

Table I. Comparison of patient, tumour and treatment characteristics between patients receiving complete adjuvant chemotherapy and no or incomplete adjuvant chemotherapy.

	Complete adjuvant chemotherapy n = 85	No or incomplete adjuvant chemotherapy n = 118	p-Value
Age, years (median, range)	63 (34–78)	70 (47–84)	
Age > 75 years	4	33	
Gender			
Male	47	61	p = 0.716
Female	38	57	
Procedure			
Pancreatoduodenectomy	75	92	
Distal pancreatectomy	8	18	p = 0.14
Total pancreatoduodenectomy	2	8	
Concomitant vascular resection	14	24	p = 0.607
Postoperative complication, any grade	39	69	p = 0.103
Postoperative major complication	9	32	p = 0.007
Tumour size (cm)	3.45	3.1	p = 0.816
Tumour stage			
T1	6	5	
T2	12	15	p = 0.42
T3	66	96	
T4	1	2	
Differentiation			
G1	11	12	
G2	50	76	p = 0.95
G3/G4	24	30	
Lymph node status*			
NO	34	34	p = 0.13
N1	51	81	
Lymph node ratio*	0.06	0.14	p = 0.043
Margins			p = 0.009
R0	49	45	
R1	36	73	
Initial recurrence pattern			
Local only	14	30	
Distant only	31	45	p = 0.59
Combined local and distant	17	25	

*Missing data in three patients

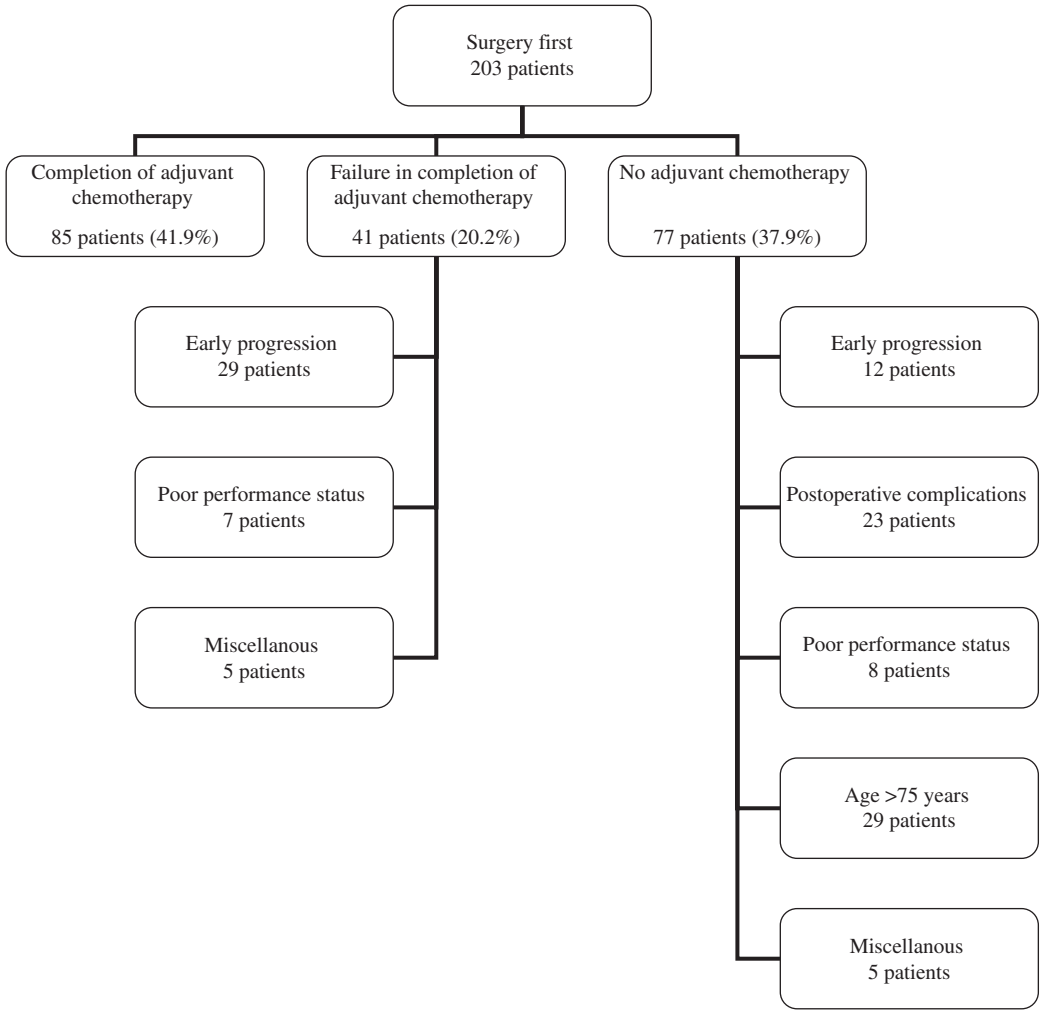

Figure 1. Reasons for not initiating or completing adjuvant chemotherapy.

but did not complete AC was five (2.5 months). Of 37 patients > 75 years, six patients initiated AC, and four patients completed it. Of 41 patients with PMC, 16 initiated AC, and nine patients completed it. In contrast, of 162 patients without PMC, 110 patients initiated AC, and 76 patients completed it (initiation rate 39% vs. 68%, $p = 0.001$, completion rate 22% vs. 47%, $p = 0.007$). PMC or poor performance status after surgery were the direct cause of not initiating or completing chemotherapy in 38 (18.7%) patients. Side effects of chemotherapy were the direct reason for discontinuation of chemotherapy in four patients only (neutropenia n = 1, thrombocytopenia n = 1, perforated peptic ulcer n = 1, toxic liver damage n = 1).

Recurrence

In total 162 patients had recurrences, whereas 41 patients were free of recurrence at time of last follow-up. Median follow-up time was 16 (range 1–95) months. The initial recurrence pattern was local only in 44 patients (27.2%), combined local and distant in 42 (25.9%), and distant only in 76 (46.9%). In 41 patients with early disease progression that precluded initiation or completion of MMT, the recurrence patterns were local only in eight patients (19.5%), combined local and distant in 11 (26.8%), and distant alone in 22 (53.7%).

Patient survival

Median OS was 17.0 (95% CI 14.6–19.4) months (Figure 2a). Median OS in patients who initiated AC was higher than in patients who did not [20.0 (95% CI 17.3–22.7) months vs. 13.0 (95% CI 10.7–15.3) months, $p < 0.001$] (Figure 2a). Median OS in patients who completed AC was higher than in patients who did not [25.0 (95% CI 17.9–32.1) months vs. 12.0 (95% CI 9.9–14.1) months, $p < 0.001$] (Figure 2b). Median OS stratified by reasons for having no or incomplete AC was 16.0 (95%

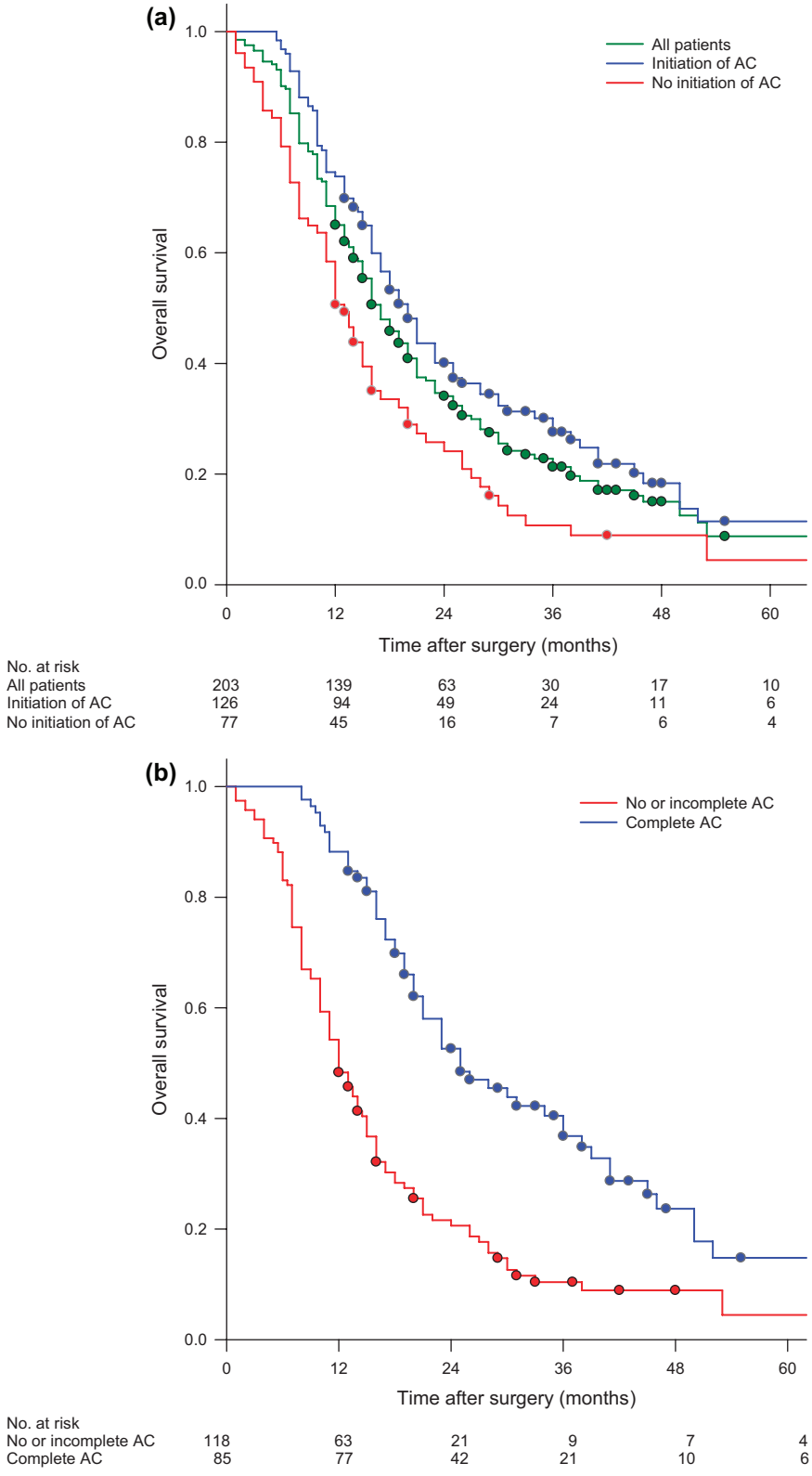

Figure 2. (a) Overall survival for patients undergoing the surgery first approach for pancreatic ductal adenocarcinoma with initiation of adjuvant chemotherapy (AC) or without initation of AC. (b) Overall survival for patients undergoing the surgery first approach for pancreatic ductal adenocarcinoma with complete adjuvant chemotherapy (AC) or with no or incomplete AC. (c) Overall survival for patients undergoing the surgery first approach for pancreatic ductal adenocarcinoma who had no or incomplete adjuvant chemotherapy stratified by reasons for not initiating or failure to complete adjuvant chemotherapy.

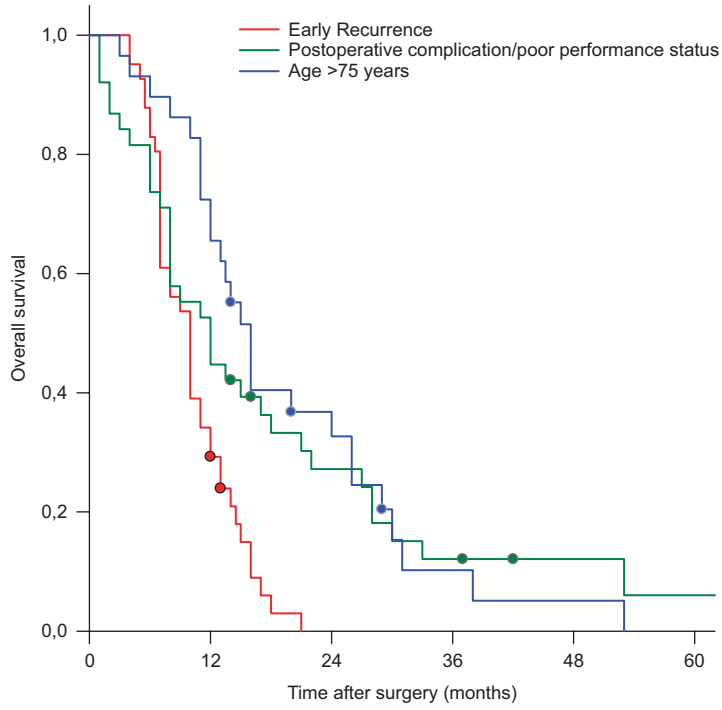

Figure 2. (Continued).

CI 13.5–18.5) months for patients with age > 75 years (n = 29), 12.0 (95% CI 7.5–16.5) months for patients with postoperative complications (any grade)/poor performance status (n = 38), and 10.0 (95% CI 8.3–11.7) months for patients with early recurrence (n = 41) ($p < 0.001$) (Figure 2c). Among all patients, PMC was associated with decreased median OS [11.0 (95% CI 7.9–14.1) months vs. 19.0 (95% CI 16.4–21.6) months, $p = 0.028$] (Figure 3). Median OS for N0 or N1 tumour or R0 resection was not influenced by PMC. However, patients with an R1 resection and PMC showed a worsened median survival of 8.0 (95% CI 3.3–12.7) months versus 16.0 (95% CI 13.7–18.3) months without PMC ($p = 0.028$).

Variables associated with reduced mortality risk are presented in Table II. When adjusted for variables that were statistically significant in univariate analyses, completion of MMT [HR 0.376, 95% CI (0.260–0.544), $p < 0.001$] and tumour grade [G1/G2, HR 0.458, 95% CI (0.310–0.678), $p < 0.001$] were the only independent prognostic factors for reduced mortality risk (Table II). Patients who completed AC reduced their mortality risk by more than 40% [HR 0.376, 95% CI (0.260–0.544)] compared to those who did not. When adjusted for competing risk of not completing AC, there was a slight improvement in cumulative survival for patients who completed AC and lived more than two years (Figure 4). Mortality risk for patients who completed AC was reduced also when adjusting for competing risk [SHR 0.426, 95% CI (0.295–0.614), $p < 0.001$], which confirmed our results from Cox regression.

Discussion

In this population-based cohort study, we report on 203 consecutive patients with resectable PDAC who underwent upfront surgery and planned AC. The study includes all cases of resectable PDAC arising in a well defined population of approximately 2.8 million people during seven years of inclusion. In addition, follow-up data are complete, and the national guidelines on resectability and AC in PDAC have routinely been adopted by surgeons and medical oncologists in this catchment area [17]. Our study shows that patients who completed all MMT had a median OS more than twice as long as patients with no or incomplete adjuvant therapy.

Obviously, the patients who completed AC had to live at least six months longer. Therefore, we have fitted a competing risk model to adjust for informative censoring. When plotting cumulative incidence adjusted for competing risk the figure revealed that

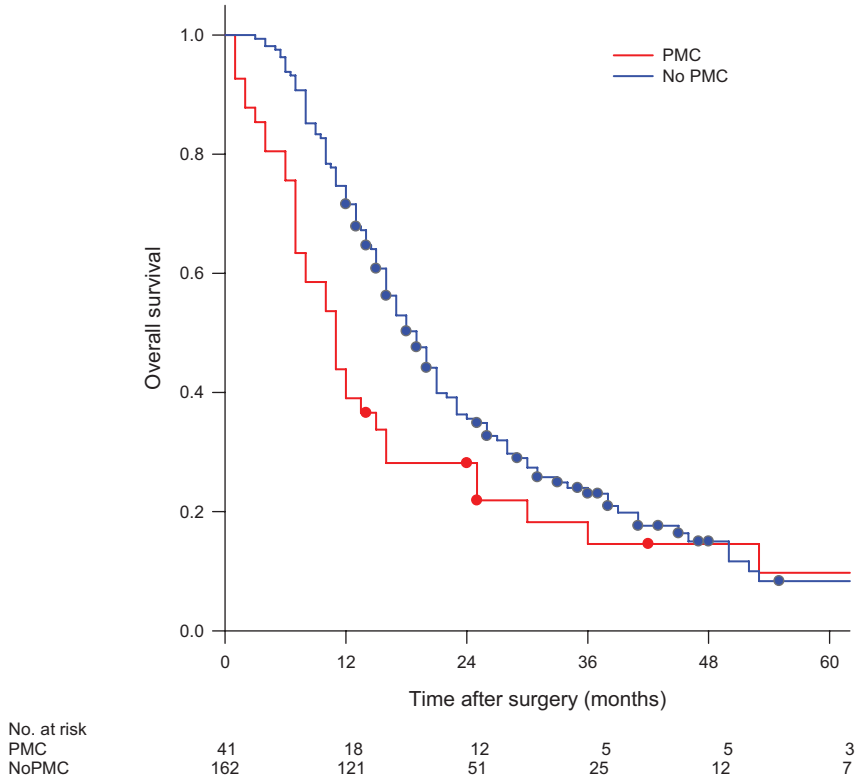

Figure 3. Overall survival for patients undergoing the surgery first approach for pancreatic ductal adenocarcinoma with postoperative major complications (PMC) or without PMC.

the survival gain was larger than the above mentioned six months. The mortality risk for those who ompleted AC remained reduced in a similar way as when modeled with Cox regression, thus confirming that MMT completion is strongly associated with reduced mortality.

Importantly, early disease progression, PMC, and poor performance status after surgery precluded initiation or completion of AC in more than one third of the patients, precluding patients from their best chance for potential long-term OS. Both initiation rate and completion rate of AC were significantly lower in patients with PMC. This is consistent with the conclusion of a recent national database study from the US showing that postoperative complications are strongly associated with AC omission and treatment delays [15].

The adjuvant therapy initiation rate of 62.1% is on par with other single or multi-institutional studies, especially when the stringent time table of eight weeks post-resection is taken into account (Table III) [7,11–15,18,20–29]. In three European well designed randomised controlled trials with good performance status patients and strict tumour biology inclusion criteria such as low CA 19-9 levels, the initiation rate of adjuvant therapy was a seemingly high 83–90%. However, even in these highly selected patients, only 50–62% completed MMT [11,18,24]. In the current study, median OS in patients who initiated AC was 20 months, and that is similar to the median OS reported in the ESPAC-1 and three trials of 20.1 and 23 months, respectively [11,24]. Given the significant survival benefit of AC which is well accepted as consensus, our completion rate of 41.9% and the internationally reported completion rates reported in the literature remain strikingly dismal. Our centre has practiced a relatively strict schedule with initiation of AC within eight weeks of the operation [8,11,17]. However, the recent report following up the ESPAC-3 trial suggested that any completion of AC rather than early initiation (before eight weeks) is an independent prognostic factor after resection for PDAC [6]. Accordingly, chemotherapy may be delayed up to 12 weeks in some patients, thus allowing adequate time for postoperative recovery.

The vast majority of patients who undergo potentially curative surgery for PDAC develop distant cancer recurrence [30]. Overall, distant metastasis was found during follow-up in 73% of patients in our study. Given the aggressive course of PDAC and the high likelihood for unrecognised metastatic disease present at the time of diagnosis, it has been proposed to reverse the sequencing for these patients [7,9]. Some centres consider NT sequencing to be a practical treatment strategy, enabling selection of patient physiology and tumour biology with a similar non-metastatic tumour phenotype for final pancreatic

Table II. Univariate and multivariate analyses of the prognostic variables associated with mortality risk in 203 patients undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma.

Variable	no.	Univariate HR#	95%CI	p-Value	Multiivariate HR#	95%CI	p-Value
Age							
≤70 years	105	0.683	0.497–0.936	p = 0.018			
>70 years (ref)	98	1					
Gender							
Female	95	0.820	0.601–1.119	p = 0.211			
Male (ref)	108	1					
ASA							
I+II	111	0.815	0.597–1.111	p = 0.196			
III (ref)	92	1					
Procedure							
Distal pancreatic resection	26	0.775	0.469–1.280	p = 0.320			
Whipple or total pancreatoduodenectomy (ref)	177	1					
Tumour stage							
T1/T2	38	0.615	0.406–0.931	p = 0.022			
T3/T4 (ref)	165	1					
Nodal status*							
N0	68	0.687	0.495–0.955	p = 0.025			
N1 (ref)	132	1					
Lymph node ratio*							
≤0.2	124	0.656	0.476–0.906	p = 0.010			
>0.2 (ref)	76	1					
Tumour grade							
G1/G2	159	0.466	0.329–0.662	p < 0.001	0.458	0.310–0.678	p < 0.001
G3/G4 (ref)	54	1			1		
Tumour size							
≤2 cm	25	0.592	0.357–0.982	p = 0.042			
>2 cm (ref)	178	1					
Resection margins							
R0	94	0.640	0.468–0.876	p = 0.005			
R1 (ref)	109	1					
Postoperative major complications							
No	41	0.659	0.450–0.965	p = 0.032			
Yes (ref)	162	1					
Completion of adjuvant chemotherapy							
Yes	85	0.407	0.294–0.564	p < 0.001	0.376	0.260–0.544	p < 0.001
No (ref)	118	1			1		

*Missing data in three patients; # Hazard Ratio

resection [7,9]. In addition, due to the strong relationship between complications and adjuvant therapy omission, administering chemotherapy upfront before surgery could potentially increase the number of patients who would ultimately benefit from its effects [7,15]. Thus, the impact of early cancer progression and PMC upon completion of MMT can be reduced by delivery of non-operative therapies prior to surgery [7]. As shown in a recent study, 62.7% of patients entering the NT sequencing strategy for anatomically resectable PDAC undergo pancreatic resection within a median interval of 4.0 months from the start of neoadjuvant treatment [9]. However, 23% of the patients developed distant metastases, 1.8% developed local tumour progression, and 11.5% had reduced performance status during neoadjuvant treatment, precluding resection [9]. Thus, most of these patients who failed to get resection would likely have failed to receive adjuvant therapy due to biological or recovery reasons, not even accounting for a percentage of PMC as well. Although all patients in the current study had CT-verified localised PDAC at the time of resection, 17% of the patients developed early distant metastatic disease within a median interval of four months after surgery which means that they underwent the stress of pancreatectomy for no oncologic gain. The OS of patients who do not complete adjuvant therapy despite a "potentially curative" resection is strikingly similar to that of patients with resectable PDAC who only receive chemotherapy or chemoradiation without resection [9]. This last point is important to highlight since even patients with metastatic PDAC have an opportunity for 12-month median OS duration [31]. Patients manifesting early distant recurrence are highly likely to have had occult metastases at the

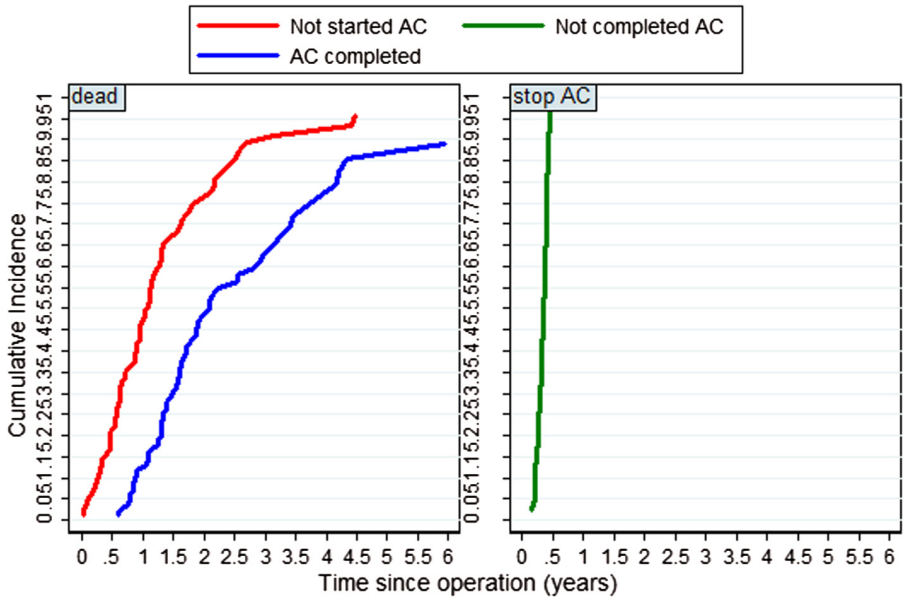

Figure 4. Cumulative survival for patients who completed adjuvant chemotherapy adjusted for competing risk.

time of resection, and may thus have been poorly selected for surgery [32]. Most predictive factors for PDAC are available only after the patient has undergone resection. Biomarkers to aid in the preoperative clinical decision making are still lacking. Hence, the development of prognostic biomarkers that can help with individualised treatment planning is of particular importance in patients with resectable PDAC.

The presence of severe complications in the postoperative period has been shown to have a strong negative impact on the long-term survival of patients with PDAC, of magnitude comparable to unfavourable tumour characteristics, such as lymph node metastasis, poor grading, or R1 status [33]. Two recent European studies suggest that postoperative severe morbidity per se had no impact on long-term survival except synergistically in patients with R1 tumour resection [34,35]. Some authors hypothesise that PMC results in impaired cellular immunity, rendering patients vulnerable to early cancer recurrence and reduced survival [35]. Our study confirms that patients with PMC and R1 resection have significantly worsened median OS, which could suggest an interaction between immunological insults from PMC and bad biology as reflected in R1 resections. The rate of R1 resections has been reported to range from as low as 18% to as high as 85% in patients undergoing SF approach in pancreatic cancer, whereas recent reports show R0 resection rates in patients with PDAC treated with a variety of neoadjuvant chemotherapy or chemoradiation protocols followed by surgery in the range 72–95%, indicating a beneficial effect of the NT strategy on margin status [36,37]. The correlations between PMC and histopathological determinants of long-term survival, such as resection margins and lymph node status, should be subjects of further research in SF and NT patients. Lastly, the impact of PMC on MMT initiation rate and OS highlights the importance of high hospital volumes in pancreatic surgery to achieve lower postoperative mortality and morbidity rates with improved long-term OS [38].

Patients aged >70 years are less likely to receive adjuvant therapy although it is associated with improved outcome [12]. In a recent study, older patients had a particularly poor outcome when adjuvant therapy was not delivered (median OS 13.1 months) [12]. In that study, the reasons for not receiving AC and whether this was specifically related to early disease progression, PMC or age per se was not discussed. In our study patients >75 years not receiving AC had a median survival of 16 months, constituting the subgroup of patients with best survival without AC. The median age of patients undergoing resection for PDAC is about 67 years [9,12,21,34]. However the median age in randomised clinical trials on AC is 60 and 61, and elderly people are clearly underrepresented in clinical trials on AC in PDAC [11,18]. As proposed by Nagrial and coworkers, increased use of adjuvant therapy in older individuals should probably be encouraged [12].

In the current study, five-year survival was 10% in the whole cohort of patients (12% in patients initiating AC, 15% in patients completing AC) which is lower than what has been found in several large studies. For example, the five-year survival rates in the largest randomised studies on AC in PDAC was 21%, 22.5% and 20%, respectively [11,18,24]. Our

Table III. Summary of selected single or multi-institutional studies from the last decade reporting adjuvant therapy initiation or completion rates for patients undergoing the surgery first approach for resectable pancreatic cancer.

Study/Year	Type of study	Sample size	MMT Initiation rate	MMT Completion rate
Labori 2015	Observational, single centre 2006–2012	CT 203	62.1%	41.9%
Tzeng 2014	Observational, single centre 2002–2007	CT 50	na	58%
Merkow 2013	ACS NSQIP/NCDB 2006–2008	CT 2047	57.7%	na
Nagrial 2013	Observational, multicentre 1990–2011	CT or CRT or RT 439	1990–2000 19.1%, 2001–2011 56.5%	na
Kooby 2013	NCDB 1998–2002	CT or CRT 11526	54.8%	na
Lewis 2013	Observational, multicentre 2001–2011	CT or CRT 424	76.4%	na
Murakami 2012	Observational, single centre 2002–2009	CT 70	100%	80%
Mayo 2012	SEER 1991–2005	CT or CRT 2461	1991–1996 40.3%, 1997–2000 51.8% 2001–2002 51.2%, 2003–2005 56.1%	na
Russ 2010	Observational, single centre 1996–2007	CT 119	67%	na
Hsu 2010	Observational, multicentre 1985–2005	CRT 1092	53.4%	na
Neoptolomos 2010	RCT, multicentre 2000–2007	CT (FLV) 551, CT (Gem) 537	88%, 89%	55%, 60%
Simons 2010	SEER 1991–2002	CT or CRT 1910	47.9%	na
Ueno 2009	RCT, multicentre 2002–2005	CT 58	98.3%	76%
Regine 2008	RCT, multicentre 1998–2002	230 CT (FLV)+CRT 221 CT (Gem)+CRT	na	87% (CT) +86.5% (CRT) 89.6% (CT) +87.3% (CRT)
Oettle 2007	Prospective RCT, multicentre 1998–2004	CT 179	90%	62%
Aloia 2007	Observational, single centre 1990–2004	CT 85	74%	na
Bilimoria 2007	NCDB 1985–2003	CT, CRT or RT 8474, CT, CRT or RT 21802	1985–1994 37.9%, 1995–2003 50.1%	na
Neoptolomos 2004	RCT, multicentre 1994–2000	CT, CRT or CT/CRT 147	83%	50%

ACS, American College of Surgeons; CRT, chemoradiotherapy; CT, chemotherapy; FLV, folinic acid/fluorouracil, Gem, gemcitabine; na, not available; NCDB, National Cancer Database; NSQIP, National Surgical Quality Improvement Program; RCT, randomised clinical trial; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results.

institution has recently shown that specialist slide review of histopathology resulted in reassignment of tumour origin in 27% of periampullary adenocarcinomas [39]. Distal bile duct cancer was most frequently misdiagnosed, and patients with distal bile duct cancer who were previously erroneously diagnosed as PDAC patients caused a falsely favourable prognosis for PDAC in the survival analysis. The large variation in reported five-year survival after pancreatoduodenectomy for PDAC in the literature (5–25%) can at least partly be explained by inaccuracies in the histopathological evaluation [39]. Some multicentre studies included good performance status patients with strict tumour biology inclusion criteria, such as low CA 19-9 levels, that also may explain the better five-years survival than in our population-based study [18]. Furthermore, population based studies generally reveal lower OS compared to selected randomised study cohorts [40].

Certain limitations of this study must be acknowledged. Most importantly, this was a retrospective analysis of patients treated at a single institution with all the inherent biases associated with this study design. However, due to the regionalisation of health care in Norway, this single-institution study is a population cohort study of a major proportion of the country with complete follow-up. In addition, the clinical database used was prospectively maintained and provided granular data on complications, surveillance, and adjuvant therapy administration, which

is nearly impossible to confirm in a typical national database. Lastly, as shown in multivariate analysis, completion of MMT and tumour grade (G1/G2) were the only independent prognostic factors ($p < 0.001$) for improved survival. Accordingly, it is important to emphasise that it is unclear whether there is a strict cause-effect relationship between completion of all therapy and prolonged survival. Certainly it is possible that patients with more favourable tumour biology live longer and therefore live long enough to complete MMT.

In conclusion, completion of MMT is strongly associated with improved OS in patients with resectable PDAC undergoing the SF sequencing strategy. Early disease progression, PMC, and poor performance status after surgery preclude MMT completion in more than one third of patients. These reasons for failure to complete MMT underscore the need for treatment sequencing strategies to increase MMT completion rates, preoperatively identification of patients at risk for manifesting early disease progression, and continued reduction of surgical morbidity, in patients who present with resectable PDAC.

Acknowledgements

This work was partially supported by the Norwegian Radium Hospital Research Foundation. All other sources of support behind this study came from the Oslo University Hospital.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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