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Systemic Neoadjuvant Chemotherapy in Modern Pancreatic Cancer Treatment: A Systematic Review and Meta-Analysis

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Abstract

Background: Pancreatic Ductal Adenocarcinoma (PDAC) remains a disease with a poor prognosis despite advances in surgery and systemic therapies. Neoadjuvant Therapy (NAT) strategies have been given increased attention and are a promising alternative to adjuvant chemotherapy. However, their role remains controversial. This meta-analysis aims to clarify the benefits of NAT in resectable PDAC.

Methods: Eligible studies were identified from MEDLINE, EMBASE, Cochrane and PubMed. Studies comparing NAT with a surgery first approach (with or without adjuvant therapy) in resectable PDAC were included. The primary outcome assessed was Overall Survival (OS). Random-effects meta-analysis was performed, as well as pooling of unadjusted Kaplan-Meier curve data.

Results: A total of 533 studies were identified that analysed the effect of NAT in PDAC. 27 studies were included in the final data synthesis. Meta-analysis suggested beneficial effects of NAT with prolonged survival compared to surgery first approach, HR 0.72 (95% CI 0.69-0.76). In addition, R0 resection rates were significantly higher in patients receiving NAT, RR 0.51 (95% CI 0.47- 0.55). Individual patient data analysis suggested that OS was better for patients receiving NAT, p=0.008.

Conclusion: Current evidence suggests that neoadjuvant chemotherapy has a beneficial effect on OS in resectable PDAC in comparison to upfront surgery and adjuvant therapy. Further trials are needed to address the need for practice change.

Keywords: Pancreas; Cancer; Neoadjuvant; Surgery

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Introduction

Pancreatic Ductal Adenocarcinoma (PDAC), the fourth largest cause of cancer-related mortality worldwide, is an aggressive malignancy with an unfavorable overall 5-year survival rate of <4% over the last two decades despite recent advances in diagnostic imaging, surgical technique and perioperative care [1]. Due to the insidious nature of PDAC the majority of patients present late with advanced, metastatic disease meaning only a small cohort of patients are surgical candidates.

The current gold standard approach for management of localised PDAC with curative intent is up-front resection of the primary tumour and regional lymph nodes followed by adjuvant chemotherapy, established based on results of previous clinical trials such as the European Study Group for Pancreatic Cancer (ESPAC)-1 trial that demonstrated a 5-year survival of 21% in patients receiving adjuvant chemotherapy versus 8% in patients who received no chemotherapy [2]. More recent studies including the ESPAC-4 [3] and the recently presented PRODIGY-24 trial [4]. Shed further light on newer adjuvant strategies that improve Disease Free Survival (DFS) and Overall Survival (OS) in PDSAC. The high morbidity rate, and subsequent prolonged recovery time, which accompanies major resectional surgery, may unfortunately have the effect of precluding patients from the timely receipt of adjuvant therapy [5]. Even for those who successfully complete surgery and adjuvant therapy, a significant proportion of patients succumb to early locoregional or systemic metastatic disease recurrence with median Overall Survival (OS) less than 20 months [6,7]. Given this dismal prognosis, many experts consider PDAC a systemic condition from onset with

Table 1: Study demographics.

Reference	Year	Country	Data source	*n*	% male	NOS score
De Geus	2017	USA	RCS	12857	35	8
Townend	2017	Austraia	RCS	195	53	8
Itchins	2017	Austraia	RCS	442	49	7
Chen	2017	Chinese	RCS	772	53.5	8
Mokdad	2016	USA	RCS	14941	51	7
Mirkin	2016	USA	RCS	18322	50.4	7
Schubert	2016	Canada	RCS	593	51.2	9
Lufti	2016	USA	RCS	7881	50.9	8
Ferrone	2015	USA	RCS	188	35.1	7
Golcher	2015	Germany	RCT	66	53	n/a
Casadei	2015	Italy	RCT	38	57.9	n/a
Roland	2015	USA	RCS	307	55	9
Fujii	2015	Japan	RCS	92	n/a	7
Sho	2014	Japan	RCS	184	53.8	8
Papavasiliou	2014	USA	RCS	309	47.6	7
Tzeng	2014	USA	RCS	167	54.5	7
Cooper	2014	USA	RCS	236	50.9	9
Papalezova	2012	USA	RCS	236	53.5	7
Barugola	2012	Italy	RCS	403	55	7
Artinyan	2011	USA	RCS	458	46.9	7
Stokes	2011	USA	RCS	170	n/a	8
Satoi	2009	Japan	RCS	68	48.5	7
Stessin	2008	USA	PCS	3885	48.3	9
Vento	2007	Finland	RCS	47	53.2	7
Al-Sukhun	2003	USA	RCT	41	43.9	n/a
White	2001	USA	RCS	111	54.1	8
Spitz	1996	USA	RCS	142	n/a	8

NOS: Newcastle-Ottawa Scale; RCS: Retrospective Cohort Study; RCT: Randomized Controlled Trial

micrometastases likely present in early stages of the disease [8].

Due to the need to improve long term survival and resectability rate, and the failure of current multimodal approaches to achieve locoregional disease control, Neoadjuvant Chemotherapy (NAT) strategies have been given increased attention and may be a promising alternative to a Surgery First (SF) approach. Numerous studies have reported beneficial effects on survival with NAT, with or without concurrent radiotherapy [9-12], but outcome data from well-designed randomized studies are limited. The hypothesised benefits of NAT include early treatment of micrometastatic disease and improved resection rates by therapeutic tumour debulking [13,14].

Despite recent meta-analyses published in this area of research, we perform a novel meta-analysis and systematic review with an enhanced secondary data analysis using an additional time-to-event data synthesis, based on the method described by Guyot et al. [15] to achieve a close approximation to the original individual patient time-to-event data from which they were generated. In this study, we investigate the effect of NAT followed by resection compared to SF approach followed by adjuvant therapy. We aim to discuss the treatment benefits of NAT in terms of overall survival.

Materials and Methods

Search strategy

A systematic review was conducted in accordance with PRISMA guidelines [16] for the reporting of meta-analyses. The literature search and data extraction was conducted independently by two authors (KR and PP) and final data including any discrepancies were resolved by consensus. A systematic search in MEDLINE (PubMed as the search engine), Embase, Web of Science and Cochrane Library was conducted using a combination of the following keywords and MeSH headings: "pancreatic cancer", "pancreatic ductal adenocarcinoma", "pancreatic tumour", "pancreatic neoplasm", "neoadjuvant therapy", "neoadjuvant", "preoperative therapy", "neoadjuvant chemotherapy", "neoadjuvant chemoradiotherapy", "resection", "operative therapy", "operation" and "surgery". All studies on patients with PDAC that provided a comparison analysis between NAT treated patients followed by curative tumour resection and primarily resected patients (Without NAT) were included.

No year of publication limits were set, and only English text publications were included. The search was last updated on January 1st, 2018. Furthermore, references of included publications were cross-checked for suitability for inclusion.

Table 2: Study details.

Reference	n (NAT)	n (no NAT)	NAT type	n (AT)	Resection rate (%)
De Geus	1541	11316	CR	n/a	n/a
Townend	42	153	GEM	42	63
Itchins	87	355	GEM,FOLFIRINOX	376	79
Chen	102	670	n/a	n/a	100
Mokdad	2005	12936	GEM	n/a	100
Mirkin	1736	16586	C, R, CR	n/a	100
Schubert	377	216	C, R, CR	39	72.4
Lufti	1184	6697	R	n/a	n/a
Ferrone	101	87	FOLFIRINOX	n/a	45.9
Golcher	33	33	GEMCAP	7	19
Casadei	18	20	GEM	4	61.1
Roland	222	85	GEM, 5-FU	25	100
Fujii	21	71	5FU	52	86
Sho	85	99	GEM	52	96
Papavasiliou	108	201	5-FU, GEMCAP	136	100
Tzeng	115	52	5-FU, GEMCAP	16	83
Cooper	153	83	CR	12	48
Papalezova	144	92	GEM	78	53
Barugola	41	362	GEMCAP, CIS	314	100
Artinyan	39	419	R	n/a	n/a
Stokes	40	130	CAP	150	40
Satoi	27	41	5-FU, CIS, GEM	0	n/a
Stessin	70	3815	5-FU, GEM	n/a	n/a
Vento	22	25	GEM	n/a	72
Al-Sukhun	20	21	5-FU, CIS	n/a	15
White	37	74	5-FU, CIS	n/a	84
Spitz	91	51	5-FU	n/a	74

NAT: Neoadjuvant Therapy; C: Chemotherapy; R: Radiotherapy; CR: Chemoradiotherapy; GEMCAP: Gemcitabine, Capecitabine; GEM: Gemcitabine; CIS: Cisplatin; CAP: Capecitabine; 5-FU: Fluorouracil; FOLFIRINOX: Folinic Acid/Fluorouracil/Irinotecan/Oxaliplatin

Following removal of duplicates, an initial review of titles and abstracts was conducted to identify articles of potential interest; these were then retrieved for full-text analysis and independent data extraction by authors conducting the literature search. Reference lists of retrieved articles were hand-searched for additional relevant references.

Selection criteria

All studies reporting data comparing outcomes for patients undergoing surgery (SF approach) (with or without adjuvant therapy), with patients undergoing NAT followed by surgery for the treatment of PDAC with curative intent were included. Studies which included data on patients with borderline resectable PDAC were included in the final analysis; however studies focusing on ampullary and periampullary cancers, unresectable or metastatic pancreatic cancer were excluded. Complications recorded in our meta-analysis were as reported and defined by the respective study authors.

Assessment of methodological quality

Study quality was assessed using the Newcastle–Ottawa Scale (NOS) [17] for cohort studies and the Cochrane Collaboration's Risk of Bias tool for RCTs [18].

The NOS assigns a score of 0–9, with points assigned on the basis of a sample's representativeness of the exposed cohort, comparability of cohorts, control for confounding factors, and appropriateness of outcome selection and reporting. Based on the methodology in previous studies, a NOS score of 7 or greater was defined as acceptable [19,20]. The Cochrane Tool considers several for each study to judge the risk of bias including: evidence of allocation concealment, extent of blinding, accounting of patients and outcome events, extent of outcome reporting, use of invalidated outcomes measures (i.e. patient reported outcomes).

Statistical analysis

Data were extracted and entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA). Meta-analysis was conducted using the logarithm of the hazard or odds ratio (HR, OR), utilising a random-effects model, in Stata (ver. 11.0, StataCorp, College Station, TX). Data heterogeneity was assessed using the I2 test, and risk of publication bias was assessed with funnel plots and Egger's test. Statistical significance was assumed at a level $p<0.05$.

Where studies reported unadjusted data in the form of Kaplan-Meier (KM) curves, we conducted an additional time-to-event data synthesis, based on the method described by Guyot et al. [15]. Using

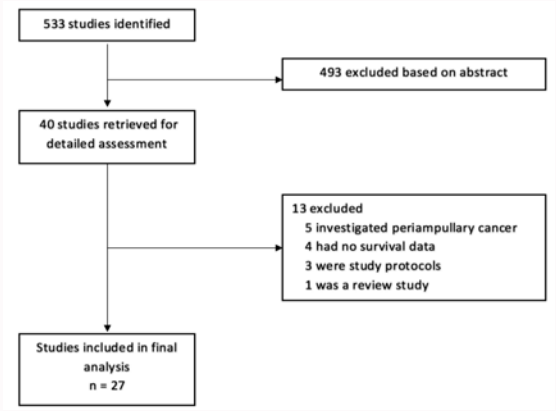

Figure 1: PRISMA flow chart of search strategy and results.

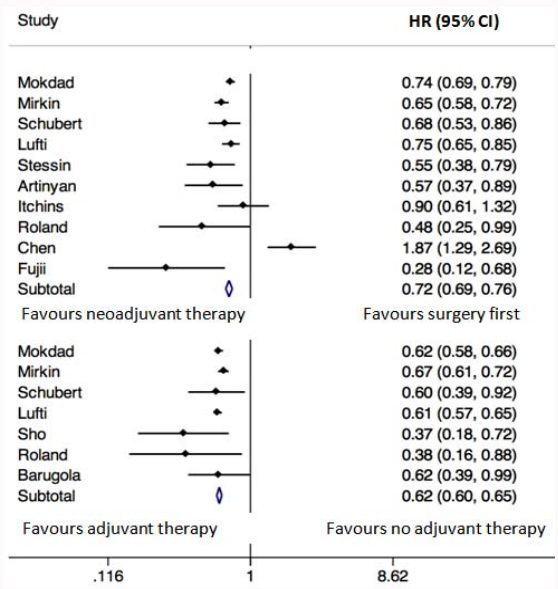

Figure 2: Forest plot of survival rates following NAT *vs.* surgery first (top), and adjuvant *vs.* no adjuvant therapy (bottom).

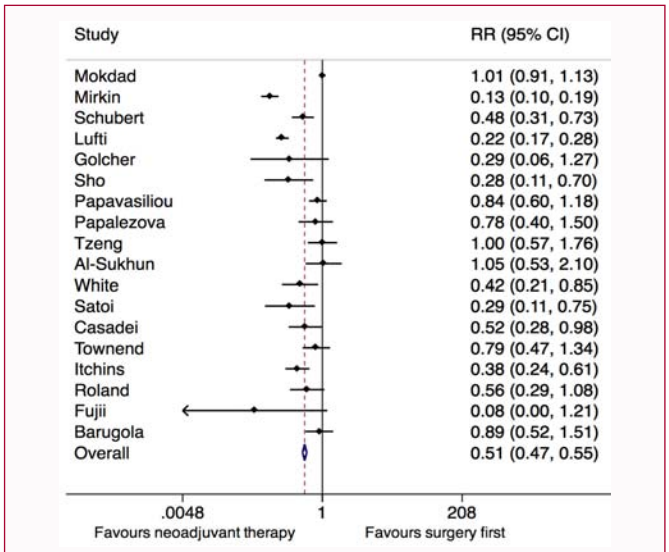

Figure 3: Forest plot of positive (R1) resection margins for patients receiving NAT *vs.* surgery first.

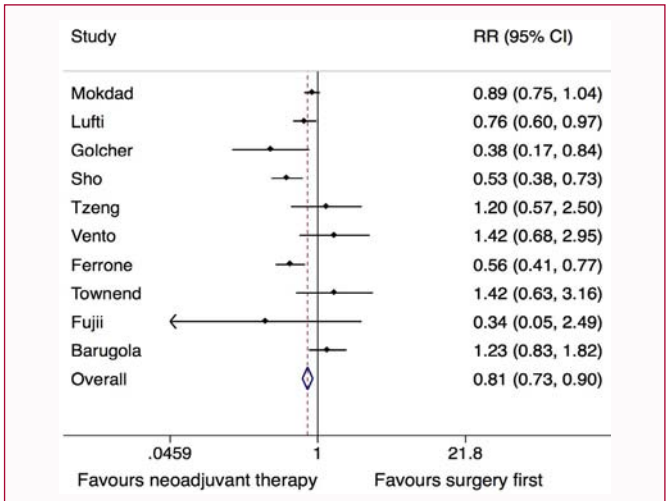

Figure 4: Forest plot of morbidity rates for NAT *vs.* surgery first.

this method, KM curve data were digitized with Engauge Digitizer (v 10.4, Mark Mitchell) thus allowing individual patient-level data to be extracted using an algorithm which assumes constant censoring, using R (v 1.0.153, RStudioInc). Reconstructed individual patient survival data were thus aggregated to create a combined survival curve, comparing the long-term outcomes of the two therapeutic strategies analyzed, using Stata.

Results

Literature research and characteristic of studies

In the initial search, 533 studies potentially relevant studies were identified, of which 493 were excluded as irrelevant after scanning titles or abstracts. A total of 40 studies were included for further full-text assessment, of which 27 studies fulfilled the inclusion criteria and were included in final data synthesis (Figure 1). Three studies were RCTs and twenty four were retrospective cohort studies.

Table 1 shows study characteristics including a quality assessment of each retrospective cohort study. The 27 studies included a total of 63,151 patients, 8,461 of which received NAT and 34,564 who were assigned to SF approach. The neoadjuvant and adjuvant therapy regimes varied greatly across each study with specific regime details not available for some studies. However, the commonly used chemotherapy/radiotherapy or chemoradiotherapy regimes included (Table 2): GEMCAP: Gemcitabine/capecitabine (4 studies, n=274), GEM: Gemictibine (10 studies, n=2590), CIS: Cisplatin (4 studies, n=125), CAP: Capcitabine (1 study, n=40), 5FU: 5-fluorouracil (9 studies, n=626), FOLFIRINOX: Folinic acid/fluorouracil/irinotecan/oxaliplatin (2 studies, n=188).

The rate of patients receiving adjuvant therapy following surgical resection was reported by 15 studies and varied between 6.2% to 88%.

Assessment of methodological quality

Study quality was moderate to high, with a median NOS of 8 (range 7-9) for cohort studies. Across the 3 RCTs included, no more than one domain for any study showed evidence of limitations as defined by the Cochrane Risk of Bias Tool, suggesting the risk of bias for these studies was low.

Meta-analysis

Meta-analysis of studies which reported HRs demonstrated better survival outcomes with NAT compared to a SF approach (Figure 2),

HR 0.72 (95% CI 0.69-0.76). Data heterogeneity was high, I2=77.9% (p<0.001).

Considering postoperative treatment regimens alone (independent of whether patients underwent NAT or not), patients receiving adjuvant therapy demonstrated better survival outcomes (Figure 2), HR 0.62 (0.60-0.65), with low data heterogeneity I2=10.7% (p=0.347).

The rate of histopathologically positive (R1) resection margins was significantly improved with NAT compared to SF, RR 0.51 (0.47-0.55), with high data heterogeneity (I2=94.3%, p<0.001) (Figure 3).

Morbidity rates was significantly reduced for patients receiving NAT compared to SF approach RR 0.81 (0.73–0.90), with high data heterogeneity (I2=66.8%, p=0.001) (Figure 4).

The risk of publication bias was visually assessed as low (Figure 5), with no significant bias risk as measured by Egger's test p=0.859.

Data synthesis of studies which did not report HRs but reported K-M curves, demonstrated improved median survival of 30.9 (95% CI 24.3-38.3) months with NAT compared to 23.8 (21.9-25.2) months with surgery first, HR 1.15 (1.00-1.33), log rank p=0.0085 (Figure 6).

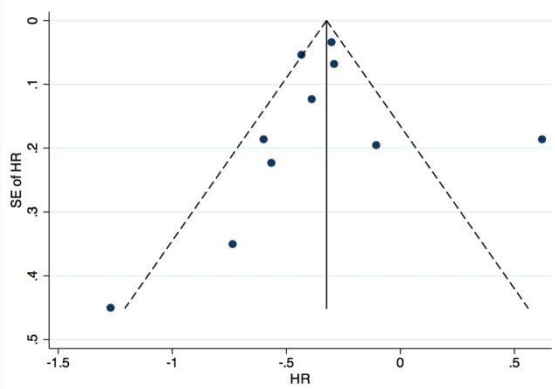

Figure 5: Funnel plot of hazard ratios for overall survival comparing NAT vs. surgery first.

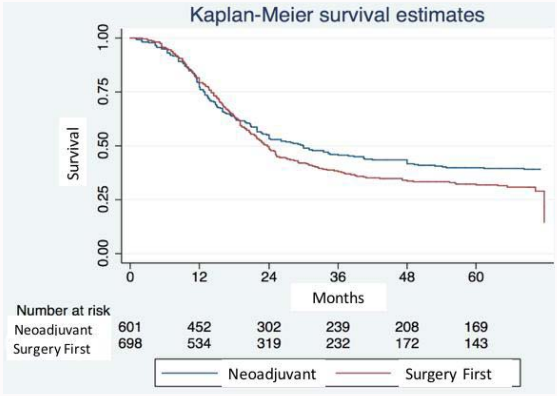

Figure 6: Kaplan Meier survival curve for Overall Survival for NAT and SF patients with PDAC with number at risk values, p=0.008.

Discussion

This systematic review and meta-analysis suggests significant survival advantage for patients receive neoadjuvant chemotherapy followed by resection with curative intent, compared to patients proceeded straight to surgery. Furthermore, there was a significant difference in survival with poorer outcomes for patients who did not receive any postoperative oncological therapy compared to those who received adjuvant chemotherapy. Similarly, histopathological results were also improved, with improved rates of R0 resection, with NAT followed by surgery.

While surgical resection is the only known curative treatment for pancreatic cancer, even in the event of R0 surgical resection there remains a local recurrence rate of 50% to 80% and a 25% to 50% chance of developing distant metastases [21–23]. To date, the reported effectiveness of adjuvant therapy has been mixed. Various phase 3 trials investigating the role of adjuvant therapy in pancreatic adenocarcinoma have shown minimal improvements in disease free survival and overall survival [22–25]. The ESPAC-3 trial [3], investigating the optimal duration and timing of adjuvant therapy in post resection pancreatic cancer, demonstrates shortcomings in adjuvant therapy by showing that only two-thirds of patients completed the full course of chemotherapy and failure to complete was associated with significantly poorer overall survival (median survival of 28.0 months versus 14.6 months). However, the recent ESPAC-4 [3] trial shows not only an improved OS with gemcitabine and capecitabine (28.0 months (95% CI 23.5–31.5)) compared with gemcitabine alone (25.5 months (22.7–27.9)) (hazard ratio 0.82 [95% CI 0.68–0.98], p=0.032)) but also a reduction in adverse events. Additionally the recently presented PRODIGY-24 trial [4] demonstrates significant improvements in DFS, OS with FOLFIRINOX, and a promising agent in neoadjuvant strategies compared with gemcitabine alone.

While adjuvant therapy has been proven to play a beneficial role in the postoperative treatment of pancreatic cancer, the significant morbidity associated with pancreatic resection means that a significant proportion of patients may fail to recover sufficiently from surgery to receive adjuvant chemotherapy within an appropriate treatment window [26]. In contrast, neoadjuvant treatment is independent of surgical morbidity and a phase II trial by Heinrich et al demonstrated the safety profile of this approach in 28 patients with resectable cancer receiving gemcitabine and cisplatin for two months before resection. The above approach showed adequate toleration to systemic therapy with minimal grade III toxicities and a low morbidity rate [27]. Furthermore, histological and cytological response showed a median survival of 26.5 months.

Neoadjuvant therapy, an evolving treatment paradigm in pancreatic cancer and already well established concepts for rectal and gastric cancer [28,29], has numerous potential benefits to address the shortcomings of adjuvant therapies. Firstly, while post-operative morbidity may subsequently preclude adjuvant therapy and reduce survival [30], this limitation is not present when administering preoperative (neoadjuvant) therapy. Secondly, preoperative therapy is hypothesised to generate free radical agents which display optimum benefit in a pre-resection, well-oxygenated environment versus a relatively hypoxic post-surgical environs [31,32]. Finally, restaging evaluation following neoadjuvant therapy and before planned surgery to detect any rapidly progressive systemic disease can serve as a means to prognosticate and risk stratify patients to determine those that may or may not benefit from radical surgical approaches. Evans has suggested that approximately 25% of patients who embark on preoperative treatment do not proceed to resection of their primary tumour due to disease progression thus sparing these patients from

the morbidity and mortality associated with surgical intervention [33].

There may also be advantages with neoadjuvant therapy with respect to post-operative complications also; at least one study reported lower rates of pancreatic leak and leak-associated morbidity and mortality [34].

However, it must be noted that the results of our meta-analysis should be interpreted with the following limitations in mind. Due to the lack of high powered randomised controlled trials, the majority of our data has been analysed from Retrospective Cohort Studies (RCS). As with most RCS, there is the inherited selection bias risk, despite relatively high study quality as measured by NOS. In this case, one must be particularly cognisant of the risk of selection bias wherein patients who failed to complete or deteriorated during neoadjuvant therapy were not clearly reported in the majority of studies. Excluding patients in the NAT cohort with toxicity or tumour progression (thereby failing to progress to surgery) in addition to including all SF patients inappropriately favors NAT. The included studies are not analysed by the 'intention-to-treat' principle and further data from prospective RCTs are needed to counter these biases.

Further to this, some of the included cohort studies are analyses of large nation-wide databases with more than 10,000 patients [11]. These studies are given a larger weight over smaller studies in our meta-analysis even when using a random-effects model. The results of the meta-analysis therefore reflect the results of these large-scale studies.

Similarly, NAT patients have not been randomized to the intervention in most included studies. Therefore, there is most likely a high selection bias in this group compared to patients undergoing direct surgery.

Additionally, multiple neoadjuvant regimes are included in the meta-analyses. Unfortunately a subgroup analyses for the different regimes was not possible due to the limited availability of specific treatment strategies provided by registries.

In recent years, advancements in pancreatic cancer management has seen the introduction of newer chemotherapeutic regimens such as FOLFIRNOX and gemcitabine-nab-paclitaxel and their subsequent integration into the neoadjuvant treatment approach. In this study we included only 2 studies using FOLFIRINOX chemotherapy. As more studies become available on this topic, this will help to further delineate the neoadjuvant therapeutic paradigm.

Our meta-analysis is limited by high data heterogeneity, and an inability to differentiate between subgroups of patients who did or did not receive adjuvant therapy (independent of NAT/surgery first), for purposes of analysis. We attempted to limit data heterogeneity by separately assessing adjusted HR data (via meta-analysis) and non-adjusted data (pooled KM-curves), with both pooled datasets producing similar results. Additional shortcomings include specific limitations of the data sources of some of the studies, such as the SEER registry and Cancer Surveillance Program database, which do not capture information such as chemotherapy regimen used or resectional margin status. However, it should be noted here that analysis of published data in the literature examining the benefit of neoadjuvant CRT for resectable pancreatic cancer, no widespread consensus exists regarding the use of radiation and CRT regimes.

Despite the promising findings of our meta-analysis, NAT does not represent a panacea in treatment of PDAC. A 2010 meta-analysis by Gillen et al found response rates of 29.1% [35] for NAT in resectable PDAC. The same study also reported no significant differences in overall survival between NAT and no-NAT patient groups, though over 20 further studies on this topic have since been published (and are included here in this review).

Further research is required before neoadjuvant treatment in resectable PDAC can be confidently recommended as the new gold standard. Further randomised trials are desirable to determine both the efficacy of NAT, but also the most effective neoadjuvant chemotherapy regimen. A recent German randomized controlled trial comparing NAT with straight-to-surgery for PDAC was terminated early due to poor accrual of patients [36]. Going forward, multi-centre trials will be required to achieve sufficient sample sizes and successful patient recruitment. To this end, we await the results of the ongoing randomized, controlled, multi- centre randomized phase III PREOPANC trial by the Dutch Pancreatic Cancer Group (DPCG) [37] and further multicentre feasibility trial (ESPAC 5F) is currently recruiting the UK.

Conclusion

This review represents a contemporaneous and comprehensive review regarding the role of neoadjuvant therapies in resectable pancreatic using the best available evidence for resection rates and survival estimates. On the basis of current evidence, it would appear that resection and survival rates after neoadjuvant therapy and surgery are improved compared to treatment with surgery alone. The overall 5 year survival of pancreatic cancer has remained virtually static at approximately 5% since the 1970s despite surgical, oncological, and technological advances over the years. This is in stark contrast to the prognosis of several other solid cancers which have seen significant improvements in the same time period. There remains a strong need for high-quality, randomized prospective studies investigating the role of neoadjuvant therapies in pancreatic cancer.

Highlights

- Pancreatic ductal adenocarcinoma (PDAC) remains a disease with a poor prognosis despite advances in surgery and systemic therapies.
- This meta-analysis aims to clarify the benefits of NAT (Neo-adjuvant therapy) in resectable PDAC.
- A met-analysis of 27 studies revealed that NAT was associated with prolonged survival compared to surgery first approach.
- R0 resection rates were significantly higher in patients receiving NAT and that OS was better for patients receiving NAT.

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