Systematic review

Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer

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Background: **Studies comparing upfront surgery with neoadjuvant treatment in pancreatic cancer may report only patients who underwent resection and so survival will be skewed. The aim of this study was to report survival by intention to treat in a comparison of upfront surgery *versus* neoadjuvant treatment in resectable or borderline resectable pancreatic cancer.**

Methods: **MEDLINE, Embase and the Cochrane Library were searched for studies reporting median overall survival by intention to treat in patients with resectable or borderline resectable pancreatic cancer treated with or without neoadjuvant treatment. Secondary outcomes included overall and R0 resection rate, pathological lymph node rate, reasons for unresectability and toxicity of neoadjuvant treatment.**

Results: **In total, 38 studies were included with 3484 patients, of whom 1738 (49·9 per cent) had neoadjuvant treatment. The weighted median overall survival by intention to treat was 18·8 months for neoadjuvant treatment and 14·8 months for upfront surgery; the difference was larger among patients whose tumours were resected (26·1 *versus* 15·0 months respectively). The overall resection rate was lower with neoadjuvant treatment than with upfront surgery (66·0 *versus* 81·3 per cent; $P < 0·001$), but the R0 rate was higher (86·8 (95 per cent c.i. 84·6 to 88·7) *versus* 66·9 (64·2 to 69·6) per cent; $P < 0·001$). Reported by intention to treat, the R0 rates were 58·0 and 54·9 per cent respectively ($P = 0·088$). The pathological lymph node rate was 43·8 per cent after neoadjuvant therapy and 64·8 per cent in the upfront surgery group ($P < 0·001$). Toxicity of at least grade III was reported in up to 64 per cent of the patients.**

Conclusion: **Neoadjuvant treatment appears to improve overall survival by intention to treat, despite lower overall resection rates for resectable or borderline resectable pancreatic cancer.**

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Introduction

Pancreatic cancer is recognized as having an overall poor prognosis and low resection rate. Long-term survival remains limited even after tumour resection. Surgical resection with adjuvant chemotherapy is the current standard of care[1]. Recent trials[1,2] have reported improved median overall survival to 24·5–28 months with adjuvant treatment. However, these trials did not report how many eligible patients were fit enough to be randomized to receive adjuvant chemotherapy. Currently, the strongest predictors of survival include surgery with curative intent, early-stage disease and complete (R0) resection[3,4]. None of these predictors are influenced by adjuvant treatment.

In patients with resectable pancreatic cancer, a recent study[5] of Surveillance, Epidemiology, and End Results (SEER) data from nearly 4000 patients suggested a survival benefit with neoadjuvant radiotherapy with or without chemotherapy over upfront surgery with or without adjuvant treatment. However, RCTs of neoadjuvant treatment compared with upfront surgery are lacking.

Non-randomized studies evaluating neoadjuvant treatment of patients with either borderline resectable or upfront resectable pancreatic cancer often suffer from selection bias because they report survival data only for patients who eventually underwent pancreatic resection. Patients with disease progression or severe toxicity who did not undergo resection are often excluded. Moreover, patients found to have metastatic or unresectable disease at exploratory surgery are also excluded[5,6].

The aim of this study was to perform a systematic review of studies comparing median overall survival of patients who underwent upfront surgery *versus* those who underwent neoadjuvant treatment in intention-to-treat analyses.

Methods

The systematic review was performed according to the PRISMA guidelines[7]. The review was registered at PROSPERO (registration number: CRD42016049374).

Search strategy

The literature was reviewed systematically by searching in MEDLINE, Embase and the Cochrane Library for studies published between 1 January 2000 and 6 December 2016. The search strategy included the following domains of Medical Subject Heading (MeSH) terms: 'pancreatic neoplasm', 'survival', 'mortality' and 'survival analysis'; these were combined with 'AND' or 'OR'. No language restrictions were used. For the MEDLINE and Embase searches, a McMaster specific prognosis filter was applied, completed with the authors' own terminology to cover the survival concept of the search strategy. A full description of the search is available in *Appendix S1* (supporting information).

Eligibility

Studies including patients with resectable or borderline resectable pancreatic cancer, either treated by upfront surgery or with neoadjuvant treatment, and reporting median overall survival by intention to treat (based on the initial treatment assignment and not on the treatment eventually received) were included. No selection was made based on adjuvant treatment. Excluded were review articles, notes, letters, case reports (5 or fewer patients), animal studies, studies that did not report median overall survival by intention to treat, and studies that reported on only specific groups of patients (for example, those with renal impairment, older than 70 years, or with poor performance status). Studies that did not report median overall survival separately for resectable and borderline resectable pancreatic tumours were also excluded.

Study selection

Two authors screened the titles and abstracts independently for eligibility. After the first two rounds of screening, full-text screening was carried out. Disagreements were resolved by discussion and consensus achieved. Primary and secondary outcomes were extracted from the full text. If studies had an overlapping cohort, the most recent study was included.

Methodological quality

All studies were assessed for risk of bias using a standard list of 11 potential risks of bias, based on the Oxford Centre for Evidence-Based Medicine (CEBM) Critical Appraisal Skills Programme checklists for randomized trials and observational cohort studies, and the Cochrane Collaboration's tool for assessing risk of bias[8–11]. All studies were graded according to the Oxford CEBM levels of evidence[12].

Outcome measures

The primary outcome, median overall survival, was extracted from the included articles. Data on numbers of patients with (borderline) resectable pancreatic cancer, resectability criteria (for example, those of the National Comprehensive Cancer Network (NCCN) and American Hepato-Pancreato-Biliary Association (AHPBA)), and types of neoadjuvant treatment and adjuvant treatment were obtained. Secondary outcomes were: resection rate, completeness of resection (R0 resection rate, only for patients undergoing resection), pathological lymph node rate, reasons for unresectability, and toxicity of at least grade III after neoadjuvant treatment.

Statistical analyses

The weighted median overall survival was calculated for the studies reporting this information for groups with and without neoadjuvant treatment. The weighted estimate of median survival (m_p) of both groups was derived by the formula used by Gillen and colleagues[13] in a previous systematic review:

$$m_{\mathrm{p}} = \left(\sum_{i=1}^{k} \frac{w_i}{m_i} \right)^{-1}$$

where m_i denotes the median survival in a study population i (with i ranging from 1 to k, where k is the number of included studies) and w_i refers to a study-specific weight function. The number of study participants (divided by

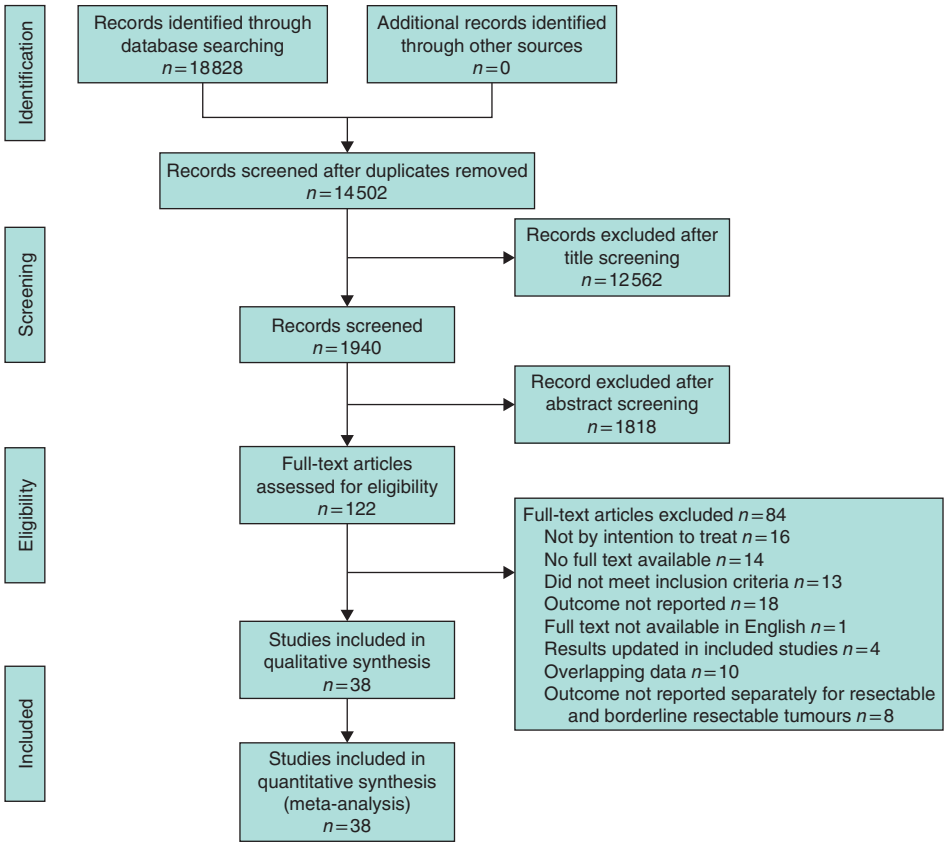

Fig. 1 PRISMA flow chart showing selection of articles for review

the total number of evaluable patients) was used as the weight.

The overall resection rate and the R0 rate for both groups were also calculated. The R0 rate was calculated for all patients and also for those who actually underwent resection of the pancreatic cancer. For both the overall resection rate and the R0 rate, the 95 per cent confidence interval was calculated using a proportion calculator[14]. The significance of differences in proportions was assessed by means of two-tailed Fisher's exact test, with a significance level $\alpha = 0{\cdot}050$, using SPSS® version 22.0.0.2 (IBM, Armonk, New York, USA).

Results

A total of 18 828 records were identified, of which 122 screened were fully. Finally, 38 studies[15–52] were included, with 3484 patients (*Fig. 1*). Study characteristics are summarized in *Tables 1* and *2*. Three RCTs, nine phase I or II trials, 12 prospective cohort studies and 14 retrospective cohort studies were included. The range of median age was 61·9–69·0 years in the upfront surgery group and 59–73 years in the neoadjuvant group (*Tables 3* and *4*). Overall, neoadjuvant treatment was administered to 1723 of 1738 patients (99·1 per cent). All studies used at least chemotherapy as neoadjuvant treatment, usually including gemcitabine (26 of 35 studies). Radiotherapy was given as part of the neoadjuvant treatment in 29 of 35 studies. No study used radiotherapy as the sole neoadjuvant treatment. The radiation dose ranged from 30 to 54 Gy.

Adjuvant therapy was initiated in ten of 12 upfront surgery studies, and 68·6 per cent of patients who underwent resection started adjuvant treatment. In the neoadjuvant treatment group, adjuvant therapy was initiated in 18 of 35 studies, and 31 per cent of patients who had resection of the pancreatic tumour started adjuvant therapy. Fewer studies reported the numbers of patients who completed adjuvant therapy (*Tables 1* and *2*).

Methodological quality

Results of the methodological quality assessment of all studies are reported in *Tables S1–S3* (supporting information). Most studies were retrospective (14) or

Table 1 Characteristics of 12 included studies that reported median overall survival after upfront surgery

Reference	No. of patients	Country	Study design	Tumour	R0 criteria (mm)*	Adjuvant treatment initiated (%)†	Adjuvant treatment completed (%)
Casadei *et al.*[15]	20	Italy	RCT	R	> 1	22	n.r.
Golcher *et al.*[16]	33	Germany	RCT	R	n.s.	44	n.r.
Bao *et al.*[17]	78	USA	Prospective	R	n.s.	78	n.r.
Raptis *et al.*[18]	102	UK	Prospective	R	n.r.	n.r.	n.r.
Tzeng *et al.*[19]	52	USA	Prospective	R	n.s.	n.r.	60
Fujii *et al.*[20]	71	Japan	Prospective	BR	> 1	100	42
Fujii *et al.*[21]	233	Japan	Prospective	R	> 1	69	45·6
Barbier *et al.*[22]	85	France	Retrospective	R	> 1	58	n.r.
Papalevoza *et al.*[23]	92	USA	Retrospective	R	n.s.	Adjuvant CRT: 66	n.r.
Kato *et al.*[24]	624	Japan	Retrospective	BR	n.s.	78·7 Adjuvant CT only: 69·9	n.r.
Hirono *et al.*[25]	331	Japan	Retrospective	R + BR	0	BR-A: 84·5	76
Murakami *et al.*[26]	25	Japan	Retrospective	BR	n.s.	48	n.r.

*Definition of R0: > 1, more than 1 mm clearance from each margin; 0, no cancer cells along any margin. †Among patients who underwent resection of pancreatic cancer. R, resectable; n.r., not reported; n.s., not specified; prospective, prospective cohort study; BR, borderline resectable; retrospective, retrospective cohort study; CRT, chemoradiotherapy; CT, chemotherapy; BR-A, borderline resectable with arterial involvement.

Table 2 Characteristics of the 35 included studies that report median overall survival after neoadjuvant treatment

Reference	No. of patients	Country	Study design	Tumour	R0 criteria (mm)*	Neoadjuvant treatment	Adjuvant treatment initiated (%)†	Adjuvant treatment completed (%)
Palmer *et al.*[27]	50	UK	RCT	R	n.s.	CT	n.r.	n.r.
Casadei *et al.*[15]	18	Italy	RCT	R	> 1	CRT	75	n.r.
Golcher *et al.*[16]	33	Germany	RCT	R	n.s.	CRT	37	n.r.
Evans *et al.*[28]	86	USA	Phase II	R	0	CRT	n.r.	n.r.
Heinrich *et al.*[29]	28	Switzerland	Phase II	R	n.s.	CT	n.r.	n.r.
Le Scodan *et al.*[30]	41	France	Phase II	R	n.s.	CRT	n.r.	n.r.
Turrini *et al.*[31]	34	France	Phase II	R	0	CRT	n.r.	n.r.
Small *et al.*[32]	17	USA	Phase II	R + BR	n.s.	CRT	n.r.	n.r.
Esnaola *et al.*[33]	13	USA	Phase II	BR	n.s.	Mixed	n.r.	n.r.
Kim *et al.*[34]	62	USA	Phase II	R + BR	n.s.	CRT	63	92
O'Reilly *et al.*[35]	38	USA	Phase II	R	n.s.	CT	96	89
Shaib *et al.*[36]	13	USA	Phase I	BR	n.s.	CRT	n.r.	n.r.
Calvo *et al.*[37]	15	Spain	Prospective	R	n.s.	CRT	n.r.	n.r.
Ohigashi *et al.*[38]	38	Korea	Prospective	BR	n.s.	CRT	100	100
Katz *et al.*[39]	22	USA	Prospective	BR	0	CRT	67	90
Oh *et al.*[40]	38	Korea	Prospective	BR	n.s.	CRT	61	n.r.
Tzeng *et al.*[41]	141	USA	Prospective	BR	n.s.	CRT	n.r.	n.r.
Tzeng *et al.*[19]	115	USA	Prospective	R	n.s.	CRT	7·8	n.r.
Fujii *et al.*[20]	21	Japan	Prospective	BR	> 1	CRT	100	56
Fujii *et al.*[21]	40	Japan	Prospective	R	> 1	CRT	83	56
Ielpo *et al.*[42]	11	Spain	Prospective	BR	n.s.	CT	100	n.r.
Masui *et al.*[43]	18	Japan	Prospective	BR	> 1	CT	93	n.r.
Takai *et al.*[44]	32	Japan	Retrospective	R	n.s.	CRT	n.r.	n.r.
Barbier *et al.*[22]	88	France	Retrospective	R	> 1	CRT	n.r.	n.r.
Patel *et al.*[45]	18	USA	Retrospective	BR	0	CRT	n.r.	n.r.
Papalevoza *et al.*[23]	144	USA	Retrospective	R	n.s.	CRT	32·9	n.r.
Chuong *et al.*[46]	57	USA	Retrospective	BR	0	CRT	84	n.r.
Dholakia *et al.*[47]	50	USA	Retrospective	BR	0	CRT	42	n.r.
Boone *et al.*[48]	61	USA	Retrospective	R + BR	n.s.	Mixed	n.r.	n.r.
Rose *et al.*[49]	64	USA	Retrospective	BR	> 1	CT/CRT	90	n.r.
Moningi *et al.*[50]	14	USA	Retrospective	BR	n.s.	CRT	n.r.	n.r.
Sho *et al.*[51]	99	Japan	Retrospective	R + BR	n.s.	CT/CRT	n.r.	R: 75 BR-V: 49 BR-A: 31
Rashid *et al.*[52]	121	USA	Retrospective	BR	0	CRT	n.r.	n.r.
Hirono *et al.*[25]	46	Japan	Retrospective	BR	0	Mixed	85	61
Murakami *et al.*[26]	52	Japan	Retrospective	BR	n.s.	CT	79	n.r.

*Definition of R0: > 1, more than 1 mm clearance from each margin; 0, no cancer cells along any margin. †Among patients who underwent resection of pancreatic cancer. R, resectable; n.r., not reported; n.s., not specified; CT, chemotherapy; CRT, chemoradiotherapy; BR, borderline resectable; prospective, prospective cohort study; retrospective, retrospective cohort study; BR-V, borderline resectable with venous involvement; BR-A, borderline resectable with arterial involvement.

Table 3 Median overall survival, resection rate and R0 rate after upfront surgery reported in 12 studies

Reference	No. of patients	Median age (years)	Median OS (months)	Resection rate, ITT (%)	R0 rate* (%)	Patients with positive lymph nodes (%)*
Casadei *et al.*[15]	20	67·5	19·5	75	33	87
Golcher *et al.*[16]	33	65·1	14·4	70	70	57
Bao *et al.*[17]	78	68†	17·9	77	75	58
Raptis *et al.*[18]	102	64‡	12	32·7	n.r.	n.r.
Tzeng *et al.*[19]	52	61·9	25·3	92	81	81
Fujii *et al.*[20]	71	63	13·1	70	40	92
Fujii *et al.*[21]	233	67	23·5	87·6	70·1	71
Barbier *et al.*[22]	85	64	17	79	67	64
Papalezova *et al.*[23]	92	65†	13	74	79	62
Kato *et al.*[24]	624	63·8	12·6	86·4	65·9	57
Hirono *et al.*[25]	331	R: n.r. BR-V: n.r. BR-A: 69§	R: 20·9 BR-V: 16·3 BR-A: 12·4	R: 89·5 BR-V: 92 BR-A: 83·1	R: n.r. BR-V: n.r. BR-A: 62·1	R: n.r. BR-V: n.r. BR-A: 74·8
Murakami *et al.*[26]	25	67§	11·6	92	17	78
Total	1746	Range 61·9–69	14·8	81·3 (79·4, 83·1)	66·9 (64·2, 69·6)	64·8 (62·0, 67·5)

Values in parentheses are 95 per cent confidence intervals. *Among patients who underwent resection of pancreatic cancer. †Mean age. ‡Including patients with unresectable pancreatic tumours, who were not reported separately. §Including patients who received neoadjuvant treatment. OS, overall survival; ITT, intention to treat; R, resectable; n.r., not reported; BR-V, borderline resectable with venous involvement; BR-A, borderline resectable with arterial involvement.

prospective (12) cohort studies. The studies showed heterogeneity in treatment and potential bias in collecting data. A common risk of bias was the heterogeneity of neoadjuvant and adjuvant treatments within and between the studies. Furthermore, there was wide variation in the duration of follow-up; in eight studies the follow-up was shorter than 12 months. In addition, different criteria were used for resectability, although most studies used the NCCN guidelines.

Three RCTs were included, one[27] of which randomized between neoadjuvant gemcitabine or gemcitabine combined with capecitabine in patients with resectable pancreatic cancer. The other two trials[15,16] randomized between neoadjuvant chemoradiotherapy and upfront surgery, but both were terminated early owing to poor accrual.

Primary outcome

The weighted median overall survival by intention to treat was 18·8 months in the neoadjuvant group and 14·8 months in the upfront surgery group.

Upfront surgery

Twelve studies[15–26] reported the median overall survival of 1746 patients undergoing upfront surgery for resectable or borderline resectable pancreatic cancer by intention to treat (*Figs 2* and *3*). Overall, 81·3 per cent of 1746 patients underwent resection, with an overall weighted median overall survival of 14·8 (range 11·6–25·3) months.

The weighted median overall survival of 819 patients with resectable pancreatic cancer was 17·7 (12–25·3) months[15–19,21–23,25], compared with 12·8 (11·6–16·3) months for 927 patients with borderline resectable pancreatic cancer[20,24–26] (*Figs 2* and *3*). In the largest (retrospective) study of Kato and colleagues[24], 63 of 624 patients (10·1 per cent) with borderline resectable pancreatic cancer also received neoadjuvant treatment and the median overall survival of these patients was not available separately. The outcome of the subgroup of patients who actually underwent resection was reported in seven[16,18,22–26] of 12 studies; the weighted median overall survival was 15·0 months for these 1048 patients (not by intention to treat).

Neoadjuvant treatment

Thirty-five studies[15,16,19–23,25–52] reported median overall survival after neoadjuvant treatment of 1738 patients with resectable or borderline resectable pancreatic cancer. The neoadjuvant regimens used are shown in *Table 2*. The weighted median overall survival was 18·8 (range 9·4–50·2) months after neoadjuvant treatment.

For the 18 studies[15,16,19,21–23,27–32,34,35,37,44,48,51] that reported the median overall survival of 857 patients with resectable pancreatic cancer, the weighted median overall survival was 18·2 (10–50·2) months (*Fig. 2*). In the 21 studies[20,25,26,32–34,36,38–43,45–52] reporting the median overall survival after neoadjuvant treatment in 881 patients with borderline resectable cancer, the weighted median overall survival was 19·2 (11–32) months (*Fig. 3*).

The outcome for the subgroup of patients who actually underwent resection was reported in 19

Table 4 Median overall survival, resection rate and R0 rate after neoadjuvant treatment reported in 35 studies

Reference	No. of patients	Median age (years)	Median OS (months)	Resection rate ITT (%)	R0 rate (%)*	Patients with positive lymph nodes (%)*
Palmer *et al.*[27]	50	66	13·6	54	74	56
Casadei *et al.*[15]	18	71·5	22·4	61	64	55
Golcher *et al.*[16]	33	62·5	17·4	58	90	32
Evans *et al.*[28]	86	65·8	22·7	74	89	38
Heinrich *et al.*[29]	28	59	26·5	89	80	64
Le Scodan *et al.*[30]	41	59·3	9·4	63	81	50
Turrini *et al.*[31]	34	61·5†	15·5	50	100	24
Small *et al.*[32]	17	62‡	R: 10·2 BR: 11·2	R: 43 BR: 30	n.r.	0
Esnaola *et al.*[33]	13	60	24·1	69	92	n.r.
Kim *et al*.[34]	62	64‡	R: 26·5 BR: 18·4	R: 57 BR: 72	85	44
O'Reilly *et al.*[35]	38	73	27·2	71	74	67
Shaib *et al.*[36]	13	64	11	62	n.r.	13
Calvo *et al.*[37]	15	61	10	60	78	n.r.
Ohigashi *et al.*[38]	38	66	32	82	97	10
Katz *et al.*[39]	22	64	21·7	68	93	33
Oh *et al.*[40]	38	59	21·2	61	78	4
Tzeng *et al.*[41]	141	63	19·1	59·6	91·7	48·8
Tzeng *et al.*[19]	115	65·5	28	82·6	89·5	51·5
Fujii *et al.*[20]	21	66	29·1	86	100	17
Fujii *et al.*[21]	40	65	24·9	90	86	39
Ielpo *et al.*[42]	11	61·8†	20	73	100	n.r.
Masui *et al.*[43]	18	63	21·7	83	87	33
Takai *et al.*[44]	32	61·8	19·2	75	n.r.	n.r.
Barbier *et al.*[22]	88	65	15	43	92	29
Patel *et al.*[45]	18	67	15·6	50	89	n.r.
Papalezova *et al.*[23]	144	64	15	53·0	78·0	25
Chuong *et al.*[46]	57	64‡	16·4	56	97	34
Dholakia *et al.*[47]	50	63·5	17·2	58	93	28
Boone *et al.*[48]	61	64‡	R: 20 BR: 22	R: 95 BR: 83	R: 86 BR: 70	n.r.
Rose *et al.*[49]	64	66	23·6	48	87	58
Moningi *et al.*[50]	14	67·2‡	14·4	29	100	n.r.
Sho *et al.*[51]	99	R: 66·4† BR-V: 66·3† BR-A: 66·0†	R: 50·2 BR-V: 26·6 BR-A: 18	R: 100 BR-V: 97 BR-A: 84	R: 98 BR-V: 97 BR-A: 81	n.r.
Rashid *et al.*[52]	121	67	17	45·5	98·4	63·6
Hirono *et al.*[25]	46	69§	18	87	80	78
Murakami *et al.*[26]	52	67§	27·1	90	72	72
Total	1738	Range 59–73	18·8 months	66·0 (63·7, 68·2)	86·8 (84·6, 88·7)	43·8 (40·6, 47·1)

Values in parentheses are 95 per cent confidence intervals. *Among patients who underwent resection of pancreatic cancer. †Mean age. ‡Including patients with unresectable pancreatic tumours, who were not reported separately. §Including patients who received upfront surgery. OS, overall survival; ITT, intention to treat; R, resectable; n.r., not reported; BR, borderline resectable; BR-V, borderline resectable with venous involvement; BR-A, borderline resectable with arterial involvement.

studies[16,19,22,23,25–31,34,37,40,41,44,46,47,52], and the weighted median overall survival was 26·1 months for these 764 patients (not by intention to treat).

Neoadjuvant chemotherapy versus *chemoradiotherapy*

Of all studies including patients who received neoadjuvant treatment, six used chemotherapy alone, 24 used chemoradiotherapy, and five used neoadjuvant chemotherapy in some patients and chemoradiotherapy in others. The weighted median overall survival was 20·9 (range 13·6–27·2) months for patients who received chemotherapy alone[26,27,29,35,42,43] and 17·8 (9·4–32) months[15,16,19–23,28,30–32,34,36–41,44–47,50,52] for chemoradiotherapy alone. Because of the heterogeneity between radiation dose and chemotherapy schedules, subset analyses should be interpreted with caution.

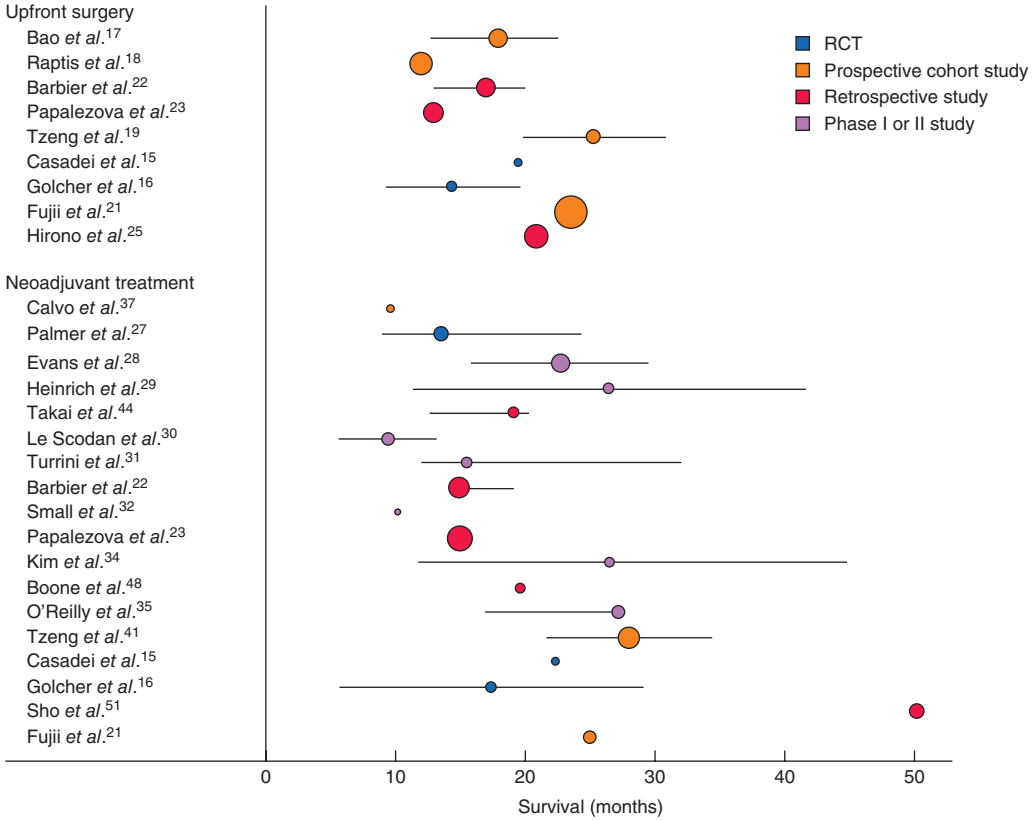

Fig. 2 Median overall survival, with 95 per cent confidence intervals, for patients with resectable pancreatic cancer after upfront surgery and after neoadjuvant treatment. The square of radius of the spheres is related to number of patients in the study

Secondary outcomes

Resection rate and R0 rate

The overall resection rate was lower in patients who had neoadjuvant treatment than in those who had upfront surgery (66·0 *versus* 81·3 per cent; $P < 0·001$).

After upfront surgery, the resection rate in all 1746 patients was 81·3 (95 per cent c.i. 79·4 to 81·3) (range 32·7–92) per cent. For patients with resectable pancreatic cancer, the resection rate was 76·8 (95 per cent c.i. 73·8 to 79·7) per cent, compared with 85·3 (82·9 to 87·5) per cent for those with borderline resectable pancreatic cancer ($P < 0·001$).

For patients who received neoadjuvant treatment, the resection rate was reported in 35 studies[15,16,20–23,25–52] and was 66·0 (95 per cent c.i. 63·7 to 68·2) (range 29–100) per cent. For patients with resectable pancreatic cancer, the resection rate was 67·0 (95 per cent c.i. 63·7 to 70·1) per cent, compared with 65·0 (61·8 to 68·2) per cent for those with borderline resectable pancreatic cancer ($P = 0·418$). The resection rate for patients in the neoadjuvant group who underwent an exploratory laparotomy was 91·2 per cent.

The R0 resection rate (only for patients who underwent resection) was higher in patients who had neoadjuvant treatment (86·8 *versus* 66·9 per cent; $P < 0·001$). The R0 resection rate was also higher with neoadjuvant treatment when the results were reported by intention to treat (58·0 *versus* 54·9 per cent; $P = 0·088$). This difference is obviously smaller, because it is the resection rate multiplied by the R0 rate.

The R0 resection rate was reported in 11 studies[15–17,19–26] after upfront surgery and was 66·9 (95 per cent c.i. 64·2 to 69·6) (range 17–81) per cent. After upfront surgery, the R0 resection rate was 71·4 per cent for patients with resectable pancreatic cancer, and 63·9 per cent for those with borderline resectable pancreatic cancer. For patients treated with neoadjuvant therapy who underwent exploratory laparotomy followed by resection, the R0 resection rate was 86·8 (95 per cent c.i. 84·6 to 88·7) (range 38·9–100) per cent. After neoadjuvant treatment, the R0 resection rate was 85·0 per cent among patients

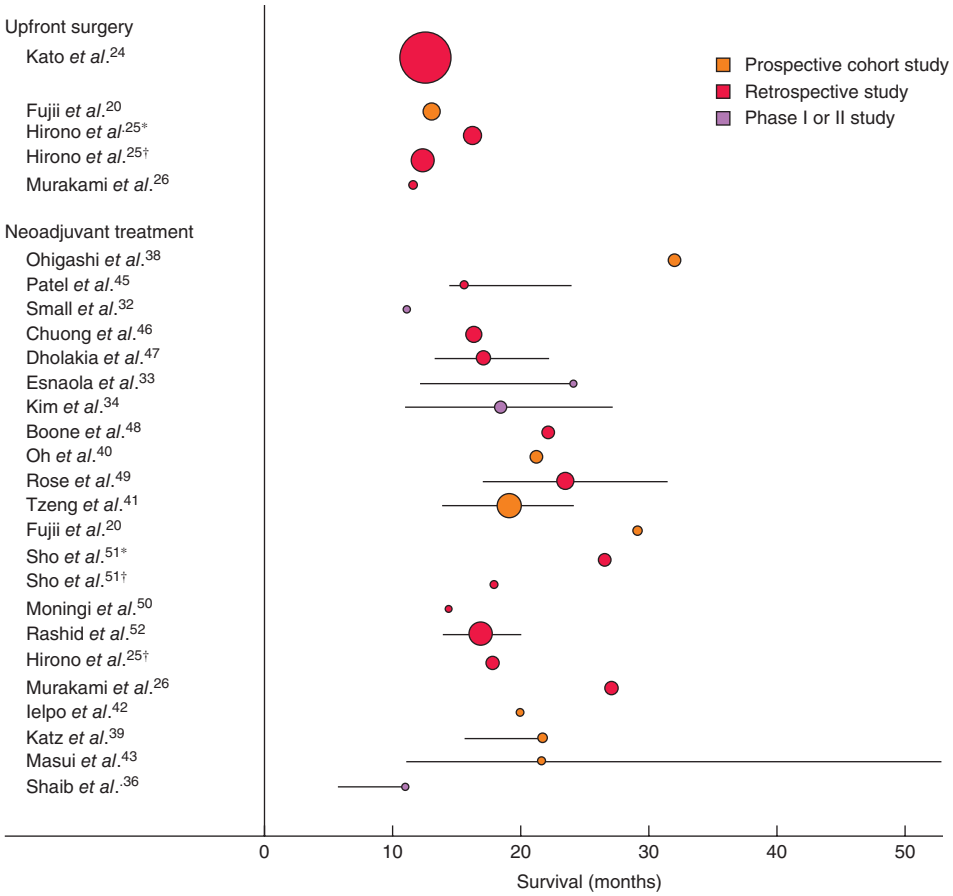

Fig. 3 Median overall survival, with 95 per cent confidence intervals, for patients with borderline resectable pancreatic cancer after upfront surgery and after neoadjuvant treatment. The square of radius of the spheres is related to number of patients in the study. *Borderline resectable owing to venous involvement; †borderline resectable owing to arterial involvement

with resectable pancreatic cancer and 88·6 per cent for those with borderline resectable cancer.

Pathological lymph node rate

The pathological lymph node rate was reported in 11 studies[15–17,19–26] after upfront surgery and was 64·8 (95 per cent c.i. 62·0 to 67·5) per cent, compared with 43·8 (40·6 to 47·1) per cent after neoadjuvant treatment in 27 studies[15,16,19–23,25–32,34–36,38–41,43,46,47,49,52]. This difference in pathological lymph node rates between the two groups was significant ($P < 0·001$).

Reasons for not performing surgery

Of the 35 neoadjuvant therapy studies, 29 reported the reason for not performing exploratory surgery. In total, 306 patients (17·8 per cent) did not proceed to exploratory surgery. Progression of disease (locally advanced or metastasis) was the most common reason for not undertaking exploratory surgery in 64·4 per cent of these patients. In total, 55 patients (18·0 per cent) could not undergo surgery because of severe side-effects or deterioration of performance after neoadjuvant treatment, representing 3·2 per cent of all patients starting neoadjuvant treatment. For the remaining patients there were other reasons, or the reason was not known. The reasons for not performing tumour resection during exploratory surgery were reported in 23 of the 35 studies (*Table S4*, supporting information). Resection was not undertaken in at least 532 patients (15·3 per cent of all 3484 included patients). The most common reason for this was distant metastasis in 42·5 per cent of these patients. Disease progression was the reason for not resecting the tumour in 25·6 per cent.

Toxicity

There was a wide range of reported toxicity of neoadjuvant treatment across studies. The most common reported adverse events were gastrointestinal (emesis, nausea and diarrhoea) and haematological (thrombopenia,

leucopenia). Toxicity of at least grade III was reported in 21 studies[15,16,20,25,27–34,36–39,42–44,46,50], with a rate of up to 64 per cent, involving mostly leucopenia, thrombocytopenia, nausea and fatigue. Katz and colleagues[39] reported a grade III toxicity rate of 64 per cent, in a study in which FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan and oxaliplatin) chemotherapy was combined with radiotherapy at a dose of 50·4 Gy. Grade IV toxicity was reported in 13 studies, and consisted mostly of haematological adverse events.

Discussion

In this systematic review, median overall survival was 18·8 months after neoadjuvant treatment *versus* 14·8 months after upfront surgery of resectable or borderline pancreatic cancer in intention-to-treat analysis. The R0 resection rate and pathological lymph node rate were also improved in the neoadjuvant group. These results suggest the superiority of neoadjuvant treatment over upfront surgery. Previous studies[13,53] reported outcomes of patients who actually underwent resection, rather than reporting by intention to treat, thus introducing a survival bias.

Median survival times for patients who actually underwent resection were 26·1 months in the neoadjuvant group and 15·0 months for upfront surgery in this review. This difference in median overall survival between the groups (11·1 months) is much bigger than the difference in the intention-to-treat analysis (4·0 months). Reporting by intention to treat reduces potential bias in treatment effect as not all patients proceed to surgery, and a large proportion of patients do not receive adjuvant chemotherapy owing to postoperative complications. Prospective phase II studies investigating the role of neoadjuvant treatment have to report on all patients included in the trial by intention to treat[54]. Therefore, for a fair comparison, upfront surgery studies and observational studies of neoadjuvant treatment should also report by intention to treat.

In the present review, 17·8 per cent of patients who had neoadjuvant treatment did not undergo exploratory surgery. This selects out patients with an aggressive pancreatic cancer that would probably have progressed in a short time after surgery anyway, thus avoiding a potentially harmful operation. In the upfront surgery group, the resection rate for patients with borderline resectable pancreatic cancer was significantly higher than that for patients with resectable tumours (85·3 *versus* 76·8 per cent respectively). This is a counterintuitive finding, as one would expect the resection rate to be higher for resectable pancreatic cancer. There is no good explanation for this finding, but the different criteria being used worldwide for assessing resectability or suboptimal preoperative assessment on CT may play a role. Centralization of pancreatic surgery has led to increased resection rates[55], but this was not investigated here.

The R0 resection rate among patients actually undergoing tumour resection was significantly better in the neoadjuvant treatment group, which is in line with the hypothesis that neoadjuvant treatment provides higher R0 rates than surgery alone[56]. The R0 resection rate after upfront surgery is comparable to rates of 29–81 per cent, depending on the R0 criteria being used, in recent large series of pancreatic cancer resection[1,57,58]. The pathological lymph node rate was also significantly different between the upfront surgery and neoadjuvant treatment groups, which may be the result of the neoadjuvant treatment causing regression of lymph node metastases[59].

No difference in surgical morbidity and mortality has been reported in studies comparing neoadjuvant treatment with upfront surgery[60–62]. A possible advantage of neoadjuvant radiation is the development of pancreatic fibrosis, which may be associated with reduced occurrence of pancreas fistula after resection[60,61,63]. Adjuvant chemotherapy is the current standard of care after resection of pancreatic cancer[1], but this treatment is often not given, or not completed, owing to a prolonged complicated postoperative course, or the preference of the patient or doctor. Data from the Netherlands Cancer Registry[64] revealed that only 54 per cent of all patients undergoing pancreatoduodenectomy received adjuvant chemotherapy, because of toxicity, age and other factors. In the present review, the toxicity reported most frequently consisted of adverse gastrointestinal and haematological events. Overall, treatment-related toxicity was given as the reason for not proceeding to exploratory surgery in only 3·2 per cent of the 1723 patients who started neoadjuvant treatment.

Median overall survival varied widely across the studies, which may be explained by the different criteria used for resectability. Most studies used the NCCN or MD Anderson Cancer Center criteria for resectability[65,66], but some studies used neither of these. Objective definitions of resectability are critical for the conduct of clinical trials of neoadjuvant treatment. Another explanation for the heterogeneity may be the variation in neoadjuvant treatment regimens across studies. The difference in receipt of postoperative adjuvant treatment (68·6 per cent in the upfront surgery group *versus* 31 per cent in the neoadjuvant group) may in part be explained by the fact that these patients had already received part or all of their systemic therapy before surgery.

The expert consensus statement of the AHPBA[67] indicates that neoadjuvant therapy provides a rational

alternative to an upfront surgery approach and could be considered in all patients with resectable pancreatic cancer. Evidence from RCTs is still lacking. The Dutch Pancreatic Cancer Group has just finished accrual of the multicentre randomized PREOPANC trial (EU Clinical Trials Register: 2012-003181-40) of neoadjuvant chemoradiotherapy *versus* upfront surgery[68]. The hypothesis is that neoadjuvant chemoradiotherapy may result in an increase in R0 resection rate and overall survival in patients with resectable or borderline resectable pancreatic cancer[68]. The trial has randomized the required 248 patients during a 4-year interval and the first results are expected in 2018. Five other randomized trials[69–73] are ongoing in Germany, Switzerland and Norway to investigate the role of neoadjuvant treatment in resectable pancreatic cancer. Two previous RCTs[15,16] from Italy and Germany were terminated early because of poor accrual.

Some limitations of the present systematic review must be taken into account. First, the quality of the included studies is moderate; the majority are retrospective studies, with high suspicion of bias. Only three studies were RCTs, and only two of these, with a total of 104 patients, randomized between upfront surgery and neoadjuvant treatment followed by surgery. Both these studies were terminated early. Owing to the clinical and methodological heterogeneity, no network analysis could be performed. Despite the limitations, the results provide the most reliable survival data, reported by intention to treat, in patients with resectable or borderline resectable pancreatic cancer.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Editor's comments

Pancreas cancer is a systemic disease, so improved control must come from a systemic approach to management. At the time of writing, several centres have already adopted liberal use of neoadjuvant chemotherapy in patients with resectable pancreatic cancer. In contrast, national guidelines in the UK and elsewhere discourage neoadjuvant chemotherapy outside clinical trials. In the current meta-analysis, and in a recent phase II trial[1] the toxicity was tolerable, but standard chemotherapy regimens have changed, which may alter safety and efficacy. Nonetheless, with such poor long-term outcome in pancreas cancer, present research does suggest that neoadjuvant chemotherapy is associated with better outcomes. Whether this simply reflects better selection of biological winners, or a genuinely improved disease control remains to be demonstrated in ongoing randomized clinical trials.

Kjetil Søreide
Editor, BJS

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