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Is there under-treatment of pancreatic cancer? Evidence from a population-based study in Ireland ☆

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ABSTRACT

Although clinical trials suggest that chemotherapy can improve survival for both resected and unresected pancreatic cancer patients, the extent to which it is used in routine clinical practice is unclear. We conducted a population-based investigation of treatment patterns and factors influencing treatment receipt and mortality for pancreatic cancer. We included 3173 patients with primary invasive pancreatic cancer, diagnosed in 1994–2003, from the National Cancer Registry (Ireland). Analysis was done by joinpoint regression, logistic regression and Cox proportional hazards. Propensity score methods were used to compare mortality in those who received chemotherapy and in 'matched' patients who did not. Seven percent of patients had a resection and 12% received chemotherapy. The resection rate did not change significantly over time and less than a quarter of patients with localised disease underwent resection. Chemotherapy use increased by 20% per annum, reaching 20% among unresected and 39% among resected patients in 2002–2003. Forty two percent of patients were untreated, and this percentage was unchanged over time. After adjusting for clinical factors, patient characteristics were significantly associated with treatment receipt; older and unmarried patients were less likely to be treated. Among resected patients, risk of death fell by 10% per annum. Chemotherapy receipt was associated with significantly reduced mortality among both surgical (hazard ratio (HR) = 0.50, 95% confidence intervals (CIs) 0.27–0.91) and non-surgical patients (HR = 0.48, 95% CI 0.38–0.61). Our findings suggest that there may be potential for extended dissemination of chemotherapy, and possibly also for greater utilisation of curative resection, in routine practice which, in turn, has potential to improve survival at the population level.

1. Introduction

More than a quarter of a million people die of pancreatic cancer worldwide each year.[1] In Europe and North America, it ranks 4th–6th among causes of cancer death.[2,3] Although patient prognosis is generally poor, variations in survival have been observed in population-based series.[3,4] Patient and tumour characteristics probably do not completely explain these findings; variations in treatment are also likely to have a role.

Surgical resection is the only potentially curative treatment for localised disease, but the procedure is complex and technically challenging.[5] Over the past 20 years, improvements in diagnostic methods, staging, pre-operative evaluation and surgical techniques, together with increased clinical specialisation, have led to significant decreases in

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post-operative mortality and morbidity, at least in large US centres.[6–10] In addition, some randomised controlled trials (RCTs) have found that adjuvant chemotherapy (with or without radiation) improves outcome post-resection,[11–14] making this the standard of care in the United States (USA),[15] although not elsewhere [e.g. United Kingdom (UK)[16,17]].

Few patients present sufficiently early to be candidates for resection. For locally advanced or metastatic disease, RCTs have demonstrated benefits of chemotherapy in terms of improved survival and quality-of-life.[18] Concurrent use of radiotherapy is controversial,[19,20] and this is reflected in different treatment guidelines in the USA[15] and the UK.[17]

How these issues play out in routine clinical practice is unclear, especially outside the USA. An increase in resection rates has been reported in the USA,[21] but the treatment rates among unresected patients are low.[22,23] Also in the USA, patients' socio-demographic characteristics have been associated with both receipt of surgery and chemotherapy.[22–24] However, most findings relate to patients diagnosed at least 10 years ago.

We investigated the extent of treatment use, recent temporal trends and factors associated with treatment receipt in a European population-based series of pancreatic cancers. We further assessed the factors affecting survival and mortality, including the influence of chemotherapy on outcome for both resected and unresected patients.

2. Methods

Details were abstracted on all individuals with invasive pancreatic cancer (ICD-O2 C25) diagnosed 1994–2003 and registered with the National Cancer Registry, Ireland (www.ncri.ie). Registration completeness is estimated to be 98%.[25] Registrations were excluded if the diagnosis was made by death certificate only or at autopsy, or if the tumour was a second malignancy (unless the first malignancy was non-melanoma skin cancer), or if occurred simultaneously with another cancer. Patients were classified by anatomical site (head, body, other specified sites and not otherwise specified), using ICD-O2 4th digits, and by SEER summary stage.[26] Summary stage was derived from TNM data which was based on pathology where available and, if not available, usually based on radiological imaging. Patients classified as 'not distant' were combined with those classified as regional disease, while those classified as 'not confined' were combined with those classified as distant disease. Based on the treatments administered within one year of diagnosis, patients were categorised by receipt of (1) pancreatic resection; (2) chemotherapy, (3) radiotherapy or (4) 'other' procedures (including stent, bypass and cholecystectomy), alone and in combination. Dates and causes of death were ascertained by linking to death certificates. Cases were followed up to death or to 31st December 2004, whichever was sooner.

Analyses were done in Stata 9.2 and SAS 9.1. Joinpoint regression was used to examine temporal trends in treatment.[27] Logistic regression was used to assess factors associated with (1) resection, and (2) among unresected patients, receipt of chemotherapy. Patients aged $\geqslant$85 were excluded since almost none received treatment. Models were adjusted for sex, region of residence (as cancer services were organised at this level in 1994–2003) and for other covariates significant on Wald-type tests (two-sided $p < 0.10$), from among age, marital status, year of diagnosis, stage, anatomical tumour site, grade and smoking status at diagnosis. Interactions between variables that were meaningful, statistically significant and that impacted on risk estimates were included. Model goodness-of-fit was assessed by the Hosmer–Lemeshow test. These models were used to compute adjusted percentages treated. Multivariate Cox proportional hazard models were run for all-cause and pancreatic cancer-specific mortality; since results were similar, only all-cause mortality was presented. Surgical and non-surgical patients were modelled separately. These models were adjusted for sex, chemotherapy and radiotherapy and for other covariates significant on Wald F-tests (two-sided $p < 0.10$). Due to non-proportional hazards, chemotherapy and radiotherapy were included as time-varying covariates with the start date of the first course taken as the index date. Kaplan–Meier curves, adjusted for age and stage, were constructed to illustrate the impact of chemotherapy (+/– radiotherapy) on survival. Since the characteristics of patients who did and did not receive chemotherapy might differ, and since these differences could affect survival (irrespective of chemotherapy receipt), we used propensity score methods to compute hazard ratios for chemotherapy receipt in surgical and non-surgical patients. These methods seek to balance the baseline (pre-treatment) characteristics (e.g. age) of the treated and untreated groups.[28] The propensity score is the probability of a case receiving treatment on the basis of his/her pre-treatment characteristics. We used logistic regression to match each patient who received chemotherapy with another who did not, but who had a similar propensity score (computed from factors including age, sex, marital status, stage, grade and anatomical site). We ran matched Cox proportional hazard regression models to compare mortality in those who received chemotherapy and in 'matched' patients who did not.

3. Results

3.1. *Patient characteristics*

The characteristics of the 3173 eligible cases are shown in Table 1. The median age at diagnosis was 72 (inter-quartile range 64–79). Diagnosis was verified histologically in 42% of cases. This proportion decreased with age (under 55: 79% verified; 55–69 years: 66%; 70–74 years: 48%; 75–84 years: 23%; 85 and older: 10%). During 1994–2003 overall, 5% of patients were recorded as having localised stage disease, 13% had regionalised disease and 46% had distant spread. The unstaged percentage decreased substantially over time, from 52% in 1994 to 23% in 2003. This was accompanied by rises in the percentages with regional (10% in 1994 to 19% in 2004) and distant (33% to 53%) diseases. The percentage with localised disease was unchanged over time.

3.2. *Treatment trends*

Overall 7% of patients underwent resection (Table 1). This percentage fell slightly, but non-significantly, from 8% in early

Table 1 – Characteristics of pancreatic cancers diagnosed in 1994–2003 and treatments received: numbers and percentages of cases.

	No.	%
Sex		
Male	1566	49.4
Female	1607	50.6
Age		
<65	828	26.1
65–74	1004	31.6
75–84	1020	32.1
85 and older	321	10.1
Period of diagnosis		
1994–1997	1237	39.0
1998–2000	933	29.4
2001–2003	1003	31.6
Marital status		
Married	1533	48.3
Not married/unknown	1640	51.7
Stage at diagnosis[a]		
Localised	157	4.9
Regional	397	12.5
Distant	1452	45.8
Not recorded	1167	36.8
Tumour location		
Head	1877	59.2
Body	210	6.6
Other specified sites	283	8.9
Not recorded	803	25.3
Histological verification		
Yes	1324	41.7
No	1849	58.3
Treatment received[b]		
Surgical resection[c]	228	7.2
Any chemotherapy	389	12.3
Chemotherapy only	226	7.1
Any radiotherapy	233	7.3
Radiotherapy only	84	2.7
Chemoradiation	145	4.6
Other treatment(s)[d]	1449	45.7
Other treatment(s) only[e]	1203	37.9
No cancer-directed treatment[f]	2532	79.8
No treatment at all[g]	1329	41.9

a Based on SEER summary stage[26]; 'regional' group also includes those classified as 'not distant'; and 'distant' group also includes those classified as 'not confined'.
b Categories not mutually exclusive; figures do not sum to 100%.
c Any pancreatic resection, including local excision, total pancreatectomy and radical pancreaticoduodenectomy.
d Stent, biliary bypass, etc.; with or without surgical resection, chemotherapy or radiotherapy.
e Those who did not have surgical resection, chemotherapy or radiotherapy, but did have other treatment(s).
f Those who did not have surgical resection, chemotherapy or radiotherapy; may, or may not, have had other treatment(s).
g Those who did not have surgical resection, chemotherapy, radiotherapy or other treatment(s).

years to 6% more recently (Fig. 1a). Of the 389 patients (12%) who received chemotherapy, 145 (37%) also had radiotherapy. Overall, use of chemotherapy rose by 20% per annum (estimated annual percentage change (EAPC) = +20.2%, 95% confidence interval (CI) 14.9–25.8%; Fig. 1a). Among unresected patients, until 1998 fewer than 6% received chemotherapy, rising to 20% in 2002–2003 (Fig. 1b). No resected patients received chemotherapy in 1994, compared to 19% in 1995–1997 and 39% in 2002–2003.

Radiotherapy use rose significantly during 1994–2000 (EAPC = +23.2%, 95% CI 17.8–28.8%), and fell in 2000–2003, although this fall was non-significant (EAPC = –5.6%, 95% CI –13.9% to +3.6%; Fig. 1a). Similar trends were evident for chemoradiation (1994–2000: EAPC = +31.4%, 95% CI 12.8–53.0%; 2000–2003: EAPC = –5.8%, 95% CI –26.9% to +21.5%).

Almost half of all the patients (46%; $n = 1449$) had other treatments, and for most (83% of 1449) this was the only treatment received. Use of other treatments alone (i.e. without

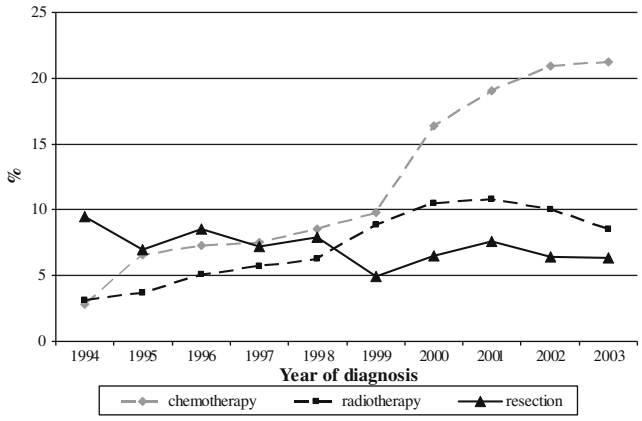

Fig. 1a – Percentages[1] of patients who had pancreatic resection, chemotherapy or radiotherapy, by year of diagnosis.

[1]Not mutually exclusive.

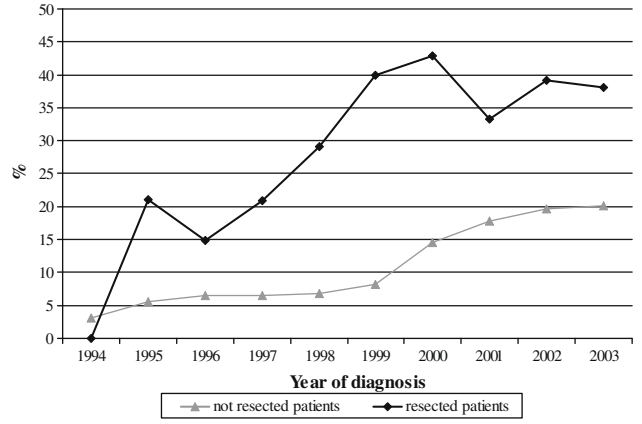

Fig. 1b – Percentage of patients who received chemotherapy [2], by year of diagnosis and surgical status.

[2]Includes chemoradiation and chemotherapy given without radiation.

chemotherapy, radiotherapy or resection) fell significantly over time (EAPC = –3.0%, 95% CI –4.8% to –1.0%). During 1994–2003, 42% of patients had no treatment at all. This proportion did not change over time (EAPC = –1.9%, 95% CI –4.2% to 0.5%).

3.3. *Factors associated with treatment receipt*

Table 2 shows factors associated with undergoing resection. There was a stage-tumour location interaction; patients with localised or regional disease (loco-regional) were most likely to undergo surgery, especially if the tumour was in the pancreas head. The likelihood of resection decreased strongly with increasing age. Patients who were not married were significantly less likely to undergo resection than married patients.

Pancreatic resections were performed by 54 clinicians in 29 different hospitals. Only two surgeons and three hospitals performed on average $\geqslant$2 resections per year, and none performed $\geqslant$5. Use of chemotherapy was significantly higher among patients undergoing resection at 'higher-volume' centres ($\geqslant$2 resections per year) than among those treated at lower volume centres (40% versus 16%).

Table 2 also shows factors associated with chemotherapy receipt among unresected patients. Those diagnosed in 2001–2003 were almost five times more likely to receive chemotherapy than those diagnosed in 1994–1997. The inverse relationship with age was even stronger than that seen among resected patients. Unmarried patients were half as likely to receive chemotherapy as married patients. Those with tumours in the pancreas body were approximately twice as likely to receive chemotherapy as those with tumours elsewhere. Odds ratios were similar for distant and loco-regional tumours, but were significantly lower for unknown stage disease.

The group receiving chemotherapy comprised two subgroups: those who received chemotherapy only (n = 244), and those who received chemoradiation (n = 145). In stratified analyses, the same factors were associated with treatment receipt in both groups (data not shown). Patients with distant stage were most likely to receive chemotherapy alone (multivariate odds ratios (ORs): distant = 1.00; loco-regional = 0.53, 95% CI 0.31–0.89; unknown = 0.44, 95% CI 0.28-0.68), whereas patients with loco-regional tumours were most likely to have chemoradiation (distant = 1.00; loco-regional = 1.99, 95% CI 1.18–3.37; unknown = 1.05, 95% CI 0.60–1.83).

3.4. *Survival and mortality*

At 1-year post-diagnosis, 13.7% of patients were still alive—49.6% of resected patients and 10.9% of unresected patients. Table 3 shows factors associated with overall mortality. For resected patients, risk of death fell over time. The strongest associations were with stage and tumour location. After adjusting for these, older patients had a significantly raised risk of death. Among unresected patients, stage and tumour site were significantly associated with mortality. Risk of death was 10% lower in female patients. Age was positively related to risk of death, but this was less pronounced in unresected patients than in surgical patients.

For both resected and unresected patients, the median survival time for those who received chemotherapy was slightly higher than for those who did not. Among resected patients, median survival was 15.8 months (inter-quartile range (IQR) 8.7–38.7) in the chemotherapy group and 11.7 months (IQR 4.2–32.1) in the group without chemotherapy. Among unresected patients, median survival for those who received chemotherapy was 3.8 months (IQR 1.9–7.2) compared to 2.3 months (IQR 1.0–5.4) for those who did not. Fig. 2 shows adjusted Kaplan–Meier survival curves stratified by resection and chemotherapy receipt. After propensity score matching, surgical patients who received chemotherapy had a significantly reduced risk of death, compared to surgical patients without chemotherapy (matched hazard ratio (HR) = 0.50, 95% CI 0.27–0.91). Among unresected patients, those who received chemotherapy had slightly higher survival up to approximately 1-year post-diagnosis. Risk of death was significantly reduced in these patients (propensity score matched HR chemotherapy receipt versus no chemotherapy = 0.48, 95% CI 0.38–0.61).

Table 2 – Factors associated with resection and chemotherapy receipt among pancreatic cancer patients diagnosed in 1994–2003: observed (obs%) and adjusted percentages (adj%), multivariate odds ratios (ORs)[a] with 95% confidence intervals (95% CIs), and p-values.[b]

	Resection[c]			Chemotherapy[d]		
	Obs%	Adj%[e]	OR (95% CI)	Obs%	Adj%[e]	OR (95% CI)
Sex						
Male	7.9	4.8	1.00	13.3	4.8	1.00
Female	8.1	5.9	1.22 (0.92–1.63) $p = 0.163$	11.7	5.3	1.11 (0.85–1.46) $p = 0.424$
Age						
<65	14.9	11.8	1.00	30.2	22.0	1.00
65–74	7.7	6.3	0.50 (0.37–0.69)	11.2	7.5	0.29 (0.22–0.38)
75–84	2.7	2.3	0.18 (0.11–0.28) $p < 0.001$	1.3	1.0	0.04 (0.02–0.07) $p < 0.001$
Marital status						
Married	10.2	6.4	1.00	19.2	7.5	1.00
Not married/unknown	5.5	4.4	0.68 (0.50–0.92) $p = 0.013$	5.8	3.3	0.42 (0.31–0.56) $p < 0.001$
Period of diagnosis						
1994–1997	8.9	6.6	1.00	6.1	2.6	1.00
1998–2000	7.0	4.6	0.68 (0.48–0.97)	10.9	4.9	1.94 (1.35–2.81)
2001–2003	7.7	4.7	0.69 (0.49–0.97) $p = 0.041$	22.1	11.2	4.78 (3.41–6.72) $p < 0.001$
*Tumour location * stage*[f]						
Head, distant	8.4	5.8	1.00			
Head, loco-regional	20.8	16.6	3.22 (2.19–4.72)			
Head, unknown	3.6	3.4	0.57 (0.34–0.97)			
Other, distant	4.8	3.2	0.53 (0.34–0.83)			
Other, loco-regional	12.2	11.3	2.05 (1.09–3.85)			
Other, unknown	6.1	5.5	0.94 (0.56–1.60) $p < 0.001$			
Tumour location						
Head				10.5	4.5	1.00
Body				22.2	9.3	2.17 (1.39–3.37)
Other				15.6	5.1	1.13 (0.73–1.76)
Unknown				13.4	5.1	1.14 (0.83–1.57) $p = 0.008$
Stage						
Distant				17.6	6.1	1.00
Loco-regional				13.0	5.3	0.86 (0.59–1.25)
Unknown				5.4	3.7	0.58 (0.41–0.83) $p = 0.011$

a ORs adjusted for factors shown in relevant column, plus health board of residence.
b Two-sided *p*-value from Wald test for coefficient of each factor in the multivariate model.
c Includes all patients aged <85 at diagnosis ($n = 2852$).
d Includes all patients aged <85, who did not have a resection ($n = 2625$).
e % Treated, adjusted for factors shown in relevant column.
f Interaction term for tumour location (head versus 'other', where 'other' includes tumours of the body and other specified sites and tumours where location is not recorded) and stage at diagnosis (loco-regional, distant, unknown).

4. Discussion

4.1. *Strengths and limitations*

This is one of the few population-based studies of pancreatic cancer treatment trends to be conducted outside the USA and to include both resected and unresected patients. Unlike most previous studies, we describe factors predicting resection and mortality in routine clinical practice rather than in specialised centres. Inclusion of patients diagnosed up to 2003 allowed examination of trends after gemcitabine was licensed in Europe (1998 in Ireland; www.imb.ie).

A substantial proportion (37%) of cases was classified as unknown stage. The medical record review conducted during the registration process, coupled with the percentages not histologically verified (58% overall) and not treated (42%), and the generally poor prognosis, suggests that these cases

Table 3 – Factors associated with risk of death among pancreatic cancer patients diagnosed in 1994–2003, and stratified by receipt of surgery: hazard ratios (HRs)[a], 95% confidence intervals and p-values.[b]

	No surgery[c]	Surgery[c]
	HR (95% CI)	HR (95% CI)
Sex		
Male	1.00	1.00
Female	0.89 (0.82–0.96)	0.82 (0.60–1.11)
	$p = 0.003$	$p = 0.199$
Age		
<65	1.00	1.00
65–74	1.25 (1.13–1.39)	1.18 (0.85–1.64)
75–84	1.54 (1.37–1.72)	2.22 (1.35–3.66)
85+	1.88 (1.61–2.18)	–
	$p < 0.001$	$p = 0.071$
Stage		
Distant	1.00	1.00
Regional	0.62 (0.54–0.70)	0.79 (0.54–1.17)
Localised	0.53 (0.44–0.64)	0.55 (0.35–0.87)
Unknown	0.69 (0.63–0.75)	0.60 (0.38–0.95)
	$p < 0.001$	$p = 0.035$
Year of diagnosis		
	–	0.90 (0.85–0.95)
		$p = 0.001$
Tumour location		
Head	1.00	1.00
Body	1.23 (1.06–1.43)	0.89 (0.37–2.12)
Other	1.40 (1.23–1.61)	0.33 (0.17–0.63)
Unknown	1.10 (1.01–1.20)	0.59 (0.38–0.90)
	$p < 0.001$	$p < 0.001$
Marital status		
Married	1.00	
Not married/unknown	1.11 (1.02–1.20)	
	$p = 0.016$	
Smoking status		
Non-smoker	1.00	
Current	0.96 (0.85–1.08)	
Ex-smoker	1.14 (1.04–1.26)	
Unknown	1.11 (1.01–1.23)	
	$p = 0.047$	

a HRs adjusted for factors shown in relevant column.
b Two-sided *p*-value from Wald test for coefficient of each factor in the multivariate model.
c Models also stratified by receipt of chemotherapy and radiotherapy, as time-dependent covariates.

were probably not fully staged at diagnosis, rather than the information not having been recorded. In addition, the decline in the unstaged percentage over time is consistent with diagnostic advances, such as CT or PET scanning and endoscopic ultrasound.[29]

Although also seen in other population-based cancer registry data from Europe and elsewhere,[4,30,31] the high proportion without histological verification raises the possibility that some cases were not true invasive cancers. Various reviews of series of purported invasive pancreatic cancers have found that a proportion actually has benign disease.[32,33] It is impossible to estimate the extent of misdiagnoses in our series, but it seems likely to be relatively small since only 5% were alive at 5 years. In addition, misdiagnoses should have fallen over time with improvements in imaging and pathology.[34]

We investigated the impact of chemotherapy on mortality and survival to determine whether advances seen in RCTs have translated into improvements for the entire patient population. Such comparisons are potentially subject to bias, and will tend to favour treatment. Although propensity score matching would be expected to attenuate the bias considerably,[28] the possibility cannot be excluded that our results are influenced by unmeasured confounders, such as performance status.

4.2. *Resection*

The percentage undergoing resection (7%) was slightly higher than the 5% reported in Scotland in 1993–1997,[30] but was relatively low when compared to other European countries during the late 1990s (11% in the Netherlands; 15% in Sweden).[35,36] Population-based studies in the USA and Sweden reported increases in resections over time,[21,36,37] which we did not find. This may be, in part, because we had lower

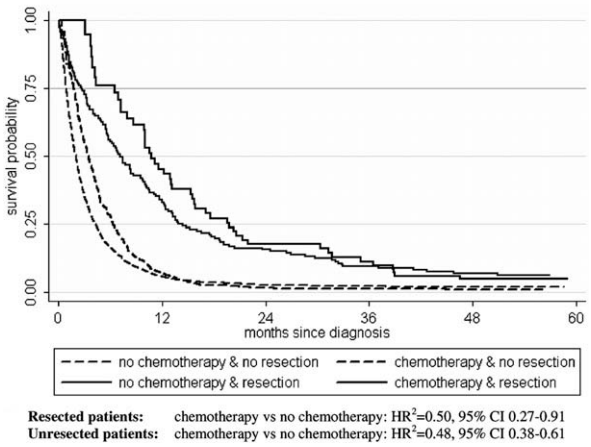

Fig. 2 – Kaplan–Meier survival curves[1] and hazard ratios (HRs)[2] with 95% confidence intervals (95% CIs), by treatment receipt, pancreatic cancer, 1994–2003.

[1]Adjusted for age and stage, with chemotherapy included as a time-dependent covariate.

[2]Propensity score matched hazard ratios; n = 52/60 resected cases successfully matched; n = 317/329 unresected cases successfully matched.

proportions of local or regional disease than in USA studies.[21,38] However, in our series, even among those with local or regional disease, only 23% and 15% underwent surgery, respectively. Although we lacked information on patients' functional status, co-morbidities, or other contraindications, it seems likely that some unresected patients with early stage disease might have been suitable for surgery. In the USA, almost 40% of stage I patients without identifiable contraindications failed to undergo surgery leading the authors to suggest that pancreatectomy was underutilised.[39] Our data support this conclusion.

Specialist management is associated with lower post-resection risk of death,[30] and treatment in a 'high-volume' unit, or by a 'high-volume' physician, improves outcomes.[40] Our setting is one of low-volume, with no surgeons or hospitals performing an average of five or more resections per year. Without further specialisation and centralisation, it would be difficult to advocate that more patients undergo surgery in Ireland. The recent establishment of managed cancer control networks and the National Cancer Control Programme, which proposes to centralise treatment, is to be welcomed. However, to optimise the numbers considered for potentially curative resection, initiatives are needed to streamline referral pathways, facilitating rapid recognition of suspicious symptoms and onward referral to specialist teams for investigation/evaluation.

Large US specialised referral centres have reported falling mortality among resected patients.[9] Our trend of decreasing risk of death over time in resected patients is consistent with this, and it is noteworthy that we saw this at the population level in a setting without strong specialisation. Several factors are likely to have contributed to improved outcomes. Advances in diagnosis and pre-operative evaluation and staging[9] have probably resulted in a better selection of patients for surgery. This would be consistent with the observed slight downward trend in the resection rate. Surgical techniques and perioperative care may also have improved.[7] In addition, the increased use of chemotherapy, which we – in common with two US population-based studies[34,37] – found to be significantly associated with reduced mortality among surgical patients, may have played a role.

4.3. *Chemotherapy use*

In US population-based studies, 25% of patients of all stages diagnosed in 1996–2000,[38] 31% of locally advanced patients diagnosed in 1991–1996[23] and 55% of resected patients diagnosed in 1994–2000,[37] received chemotherapy. These were much higher than the levels seen in our population; even after allowing for the rapid increases in use over time, in 2002–2003 only 20% of unresected and 39% of resected patients received chemotherapy. These trends suggest that there may be 'catch-up' as RCT findings, or commonly accepted US standards of care, disseminate into routine clinical practice in Europe.

Although based on small numbers, it was noteworthy that chemotherapy use among resected patients was higher in centres which conducted greater numbers of resections. This provides further evidence of under-provision of treatment, and suggests that greater specialisation or centralisation is a potential route to help reduce treatment disparities.

A Cochrane Collaboration 2006 review concluded that mortality was lower among patients with locally advanced and metastatic disease who were treated by chemotherapy as compared to best supportive care.[18] The findings were based on eight eligible RCTs, including less than 500 patients in total. All chemotherapy regimens were 5FU based, and there were variations between studies in what constituted best supportive care, and in how clinical benefit was assessed. Although there was statistical heterogeneity between the studies, in the pooled analysis the odds ratio for mortality at 12 months for chemotherapy versus best supportive care was significantly reduced (0.37, 95% CI 0.25–0.57). Our observation of a halving in the risk of death in unresected patients who received chemotherapy is remarkably consistent with this. It is also consistent with the results of two US population-based studies.[23,38] Overall, our findings suggest that there is an argument – and potential – for further dissemination of chemotherapy among patients unsuitable for resection. However, the benefits are of relatively short duration, and need to be weighed against the disadvantages (such as side-effects), bearing in mind that the relative balance of these may vary by regimen,[41] and that some patients may decline therapy if potential disadvantages are explained. Moreover, the proportion of responders is likely to be low (typically <20% in RCTs).[41]

4.4. *Untreated patients*

The proportion who had no treatment was similar to that reported in other series and, as elsewhere, did not decrease over time.[22,36,42] The untreated group comprised mainly elderly patients (56% aged ⩾75) who presented late (50% distant and 39% unknown stage). Although treatment options for

these patients are limited, it is possible that some might benefit from palliative chemotherapy. Since patients referred to more specialised clinicians are more likely to receive palliative therapy,[43] the moves towards specialisation in cancer care in Ireland may reduce the proportion of untreated patients in the future.

4.5. *Patient-related factors and treatment receipt*

After adjusting for clinical factors, age was the strongest predictor of treatment. However, advanced age alone should not preclude treatment. There is some evidence – albeit limited – that elderly patients may respond as well to gemcitabine,[44] and have as good post-resection outcomes[29,45,46] as younger patients. Thus, although previously reported in the USA,[23,39] this finding is important for several reasons. Firstly, most previous series included patients from the early 1990s or earlier, and we show that age-related treatment disparities persist in more recent years. Secondly, the likelihood of treatment was particularly low for those aged $\geqslant$75 and almost half of the cases occur in this age group. Thirdly, the relationship we observed was particularly strong suggesting that age-related treatment inequalities may be more pronounced in (some) European countries than in the USA.

It is possible that the age effect is partly an artefact. For example, older patients may be more likely to decline treatment. This has been shown in the case of surgery for early stage pancreatic cancer.[39] Information on treatment offered but declined is not routinely recorded by the National Cancer Registry Ireland, but we would anticipate that the overall proportion who decline the treatment is likely to be small and could not fully explain the association with age. Age is a strong predictor of functional decline and older patients are more likely to have serious co-morbidities which could preclude treatment. In a study of more than 1000 pancreatic cancer patients from the Netherlands diagnosed in 1995–2002, around two-thirds of those aged 65 and older had co-morbidities compared to less than 50% of those aged 50–64 years, and the authors considered that prevalence in older patients may be under-estimated.[47] We had no information on co-morbidities, so it is possible that our effect estimates for age actually reflect the combined effects of age and co-morbidity. However, Krzyzanowska et al.[23] found that the association between age and chemotherapy receipt in advanced pancreatic cancer persisted even after adjustment for co-morbid conditions. In addition, Janssen-Heijnen et al.,[32] in a study of multiple cancer types, concluded that age itself appeared to have more influence on treatment than co-morbidities.[47] What needs to be established is whether older patients are comprehensively evaluated and determined to be unsuitable for treatment on the basis of co-morbities, fraility, etc. or whether clinicians assume that: (i) because of poorer outcomes or short life expectancy, older patients should not be treated or (ii) no appropriate treatment exists for older patients.

As we have shown for other cancers,[48–50] patients who were not married were significantly less likely to be treated than those who were married. The reasons for this remain unclear. Since the association was particularly strong for chemotherapy, and chemotherapy may be especially challenging for pancreatic cancer patients, who are often very frail, it suggests that availability (or lack) of support at close-hand may be a possible explanation.

5. Conclusions

We found low rates of treatment among pancreatic cancer patients in routine clinical practice, and although chemotherapy use is increasing, patient-related factors predict treatment receipt. While recognising that not at all patients are suitable candidates for treatment, our findings suggest that there may be potential for extended dissemination of chemotherapy and possibly also for greater utilisation of curative resection. Since our findings suggest that chemotherapy is effective in both resected and unresected patients, more widespread use has the potential to bring about improvements in survival.

Conflict of interest statement

None declared.

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