Original article

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Population-based study of the impact of surgical and adjuvant therapy at the same or a different institution on survival of patients with pancreatic adenocarcinoma

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Background: **Pancreatic cancer surgery is increasingly regionalized in high-volume centres. Provision of adjuvant chemotherapy in the same institution can place a burden on patients, whereas receiving adjuvant chemotherapy at a different institution closer to home may create disparities in care. This study compared long-term outcomes of patients with pancreatic adenocarcinoma receiving adjuvant chemotherapy at the institution where they had undergone surgery with outcomes for those receiving chemotherapy at a different institution.**

Methods: **This was a population-based study of patients receiving adjuvant chemotherapy after resection of pancreatic adenocarcinoma performed at ten designated hepatopancreatobiliary centres in Ontario, Canada, between 2004 and 2014. Patients were divided into those receiving chemotherapy at the same institution as surgery or a different institution from where surgery was performed. The primary outcome was overall survival (OS). Multivariable Cox regression assessed the association between OS and each chemotherapy group, adjusted for potential confounders.**

Results: **Of 589 patients, 374 (63·5 per cent) received adjuvant chemotherapy at the same institution as surgery. After adjusting for age, sex, co-morbidity, socioeconomic status, rural living, tumour stage, margin positivity and year of surgery, the location of adjuvant chemotherapy was not independently associated with OS (hazard ratio 1·03, 95 per cent c.i. 0·85 to 1·24). For patients who underwent chemotherapy at a different institution, mean travel distance to receive chemotherapy was less (22·9 km) than that needed for surgery (106·7 km).**

Conclusion: **After pancreatectomy for pancreatic adenocarcinoma at specialized hepatopancreatobiliary surgery centres, OS was not affected by the location of the centre delivering adjuvant chemotherapy. Receiving this treatment in a local centre reduced patients' travel burden.**

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Introduction

Pancreatic adenocarcinoma is the fourth leading cause of malignancy-related death and responsible for an estimated 4800 annual deaths, with a 5-year overall survival (OS) rate of 5 per cent in North America[1]. Treatments that include surgical resection remain the only chance of achieving cure, with a 5-year survival of around 24 per cent[2,3].

Although perioperative outcomes after pancreatectomy have improved in recent decades, more than three-quarters of all patients develop recurrence after surgery with curative intent[4]. The presence of micrometastatic disease

at the time of surgery is suspected to be a major contributor to this pattern of failure. This pattern of distant recurrence has prompted treatment with adjuvant chemotherapy, which has been included in clinical practice guidelines advocating its use among patients with lymph node-positive disease, following the results of RCTs[5–7].

Contemporary cancer care includes an increased complexity of cases and the creation of specialized surgical treatment centres to improve patient outcomes by increasing volume and expertise[8]. Improved outcomes associated with increased surgeon and institutional pancreatectomy volumes have led to the regionalization of this complex surgery to high-volume centres[8–10]. Whether policy-mandated or happening naturally, regionalization of surgical care for pancreatic adenocarcinoma to high-volume centres has become a reality in many healthcare systems[11–14]. Although patients are willing to travel to high-volume centres to seek improved outcomes, they also highly value care closer to home when comparable quality of care and outcomes can be provided[15,16]. As a result, patients may receive surgery and adjuvant chemotherapy at different institutions.

Coordinating care over different institutions creates new challenges, including potentially variable institutional case-volume and expertise, along with issues pertaining to transition of care and sharing of health information. Whether patients receive their care at a single institution or multiple institutions might therefore impact on outcome. Combination of cancer care at high- and low-volume centres has been reported in up to 50 per cent of patients for other cancer types[17].

This study sought to evaluate the effect of receiving adjuvant chemotherapy at the same institution as surgery or at a different institution on long-term outcomes of patients with resected pancreatic adenocarcinoma.

Methods

Study design

A comparative population-based cohort study was performed using data from administrative databases stored at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Canada. The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board, complying with the data confidentiality and privacy guidelines of ICES.

Data sources

The Ontario Cancer Registry (OCR) includes all patients with a cancer diagnosis (excluding non-melanoma skin cancer) in Ontario since 1964[18,19]. Data reliability has been ascertained and reported previously[19–21]. The Registered Persons Database (RPDB) contains vital status and demographic data on all individuals covered under the Ontario Health Insurance Plan (OHIP)[22]. Information regarding health services provided is included in the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD) for acute inpatient hospital admissions, the National Ambulatory Care Reporting System (NACRS) for same-day surgery admissions, emergency room visits and oncology clinic visits, and the OHIP Claims Database for billing from healthcare providers, including physicians, groups, laboratories and out-of-province providers[23]. The Cancer Activity Level Reporting (ALR) database is maintained by the OCR and includes chemotherapeutics and medications administered to these patients. These databases have been validated for a variety of diagnoses and services[23].

Pathologic characteristics, including staging and margins status, were obtained using a previously established data set created by manual abstraction of pathology reports from the OCR. As reported previously[24,25], the standardized abstraction tool was based on the 2013 College of American Pathologists protocol and validated by independent dual abstraction of 15 per cent of the reports.

The data sets were linked using unique encoded identifiers and analysed at the ICES. The research team's analyst had complete access to all data sets used in this study in order to create the study cohorts, proceed to linkage and perform the analyses.

Study population and cohort

This study was conducted in all patients with a valid OHIP number from 2004 to 2015. Under the Canada Health Act, the Ontario population benefits from universally accessible and publicly funded healthcare though OHIP[26]. All residents of Ontario are eligible for OHIP after they have resided in the province for 3 months. The population of Ontario was 13 448 494 in 2016, residing in a land area of 917 741 km^2.

Specialized cancer services are regionalized in Ontario. Over the study interval, hepatopancreatobiliary (HPB) cancer surgery was confined to ten designated centres of excellence in the province, with standardized provincial requirements regarding staffing and resources to maintain this designation[27]. The centre of excellence designation is attributed by the provincial regulatory body for oncology, Cancer Care Ontario, initiated in 2004. Requirements include minimum institutional volumes for pancreatectomy and hepatectomy, the presence of a minimum of two

fellowship-trained HPB surgeons, intensive care services, and 24-h access to interventional radiology and therapeutic endoscopy.

Patients with a diagnosis of pancreatic adenocarcinoma in the OCR were identified with ICD-O.3 codes (C25.0–C25.9, and histology codes 8000, 8001, 8010, 8020, 8021, 8031, 8035, 8140, 8144, 8145, 8255, 8340, 8341, 8344, 8440, 8442, 8470, 8481, 8490, 8500, 8560, 8570, 8574, 8575, 9990). Patients undergoing pancreatoduodenectomy and distal pancreatectomy at one of the ten designated HPB centres of excellence, based on CIHI-DAD information, and receiving adjuvant chemotherapy were included. Adjuvant chemotherapy was defined using physician billing codes from OHIP for chemotherapy infusion. Patients with at least two billing codes within 150 days of surgery were categorized as receiving this treatment. The identification of chemotherapy administration using OHIP has been described previously with 90 per cent concordance between OHIP codes and patient medication records (ALR)[25,28,29]. Patients were excluded if aged less than 18 years or more than 99 years, if they had a diagnosis of another cancer before or after surgery, or if they had received neoadjuvant therapy.

Exposure

The main exposure of interest was receipt of adjuvant chemotherapy at the same institution where surgery had been performed. The surgery institution was assigned using the institution code from the OHIP and DAD databases. The chemotherapy institution was determined from the institution code from the OHIP and ALR databases. When institutions included more than one site, they were combined as a common institution (a separate surgical site where surgery was performed and cancer centre where chemotherapy was administered were combined as one institution if they belonged to the same health centre with shared resources, health records and physicians working at both sites). Patients were divided into those receiving adjuvant chemotherapy at the same institution as surgery and those receiving this systemic treatment at a different institution from where surgery had been performed.

Co-variables

Age and sex were abstracted from the RPDB. Rural living was determined by postal code of residence in a rural area based on the national census definition of a community of fewer than 10 000 people[30]. Socioeconomic status (SES) was assessed with an ecological measure of income quintile based on the median income of a patient's postal code of residence using national census data[31,32]. The co-morbidity burden was measured using the Johns Hopkins Adjusted Clinical Groups system score, abstracted from the CIHI-DAD and NACRS using ICD codes. The 32 aggregated diagnosis groups (ADG) were summed to create a total score, then dichotomized with a cut-off of 10 for high co-morbidity burden, consistent with previous reports[33,34]. Pathology details were obtained from the previously described pathology database. Straight-line distances from patients' residence to the surgical institution and to the institution providing chemotherapy were measured using latitude and longitude for those geographical points (based on Statistics Canada equations), and reported in kilometres.

Outcomes measures

OS was measured from date of surgery to the date of death according to the RPDB. The end of follow-up was defined as the date of death, the date of last contact or 31 March 2017, whichever came first, offering an opportunity for a minimum of 15 months' follow-up for all patients.

Statistical analysis

Descriptive analyses were used to define baseline characteristics and outcomes. Categorical variables were reported as absolute numbers and proportions, and continuous variables as mean(s.d.) or median (i.q.r.) values. Comparison testing was undertaken with the χ^2 test for categorical variables and *t* test or Mann–Whitney *U* test for continuous variables, as appropriate. Kaplan–Meier methods were used for OS analysis[35]. OS curves were compared between location of adjuvant chemotherapy groups with the log rank test.

A Cox multivariable regression model was constructed to assess the association of location of adjuvant chemotherapy with OS, while adjusting for other characteristics. Relevant demographic and clinical characteristics were identified *a priori* as potential confounders of the relationship between location of adjuvant chemotherapy and OS. These variables were selected based on clinical relevance (markers of complexity of cancer care) and existing literature (known relationship between pancreatic adenocarcinoma and OS)[25,36–38]. The most parsimonious set of co-variables was selected to maintain adequate study power. The following co-variables were ultimately included: age, sex, co-morbidity burden, SES, rural living, T category, N status, margins and time interval of surgery (2004–2010 *versus* 2011–2015).

Table 1 Demographic characteristics stratified by adjuvant chemotherapy institution

	Adjuvant chemotherapy at same institution as surgery ($n = 374$)	Adjuvant chemotherapy at different institution from surgery ($n = 215$)	P*
Age group (years)			0·602
≤ 60	138 (36·9)	73 (34·0)	
61–70	140 (37·4)	79 (36·7)	
≥ 71	96 (25·7)	63 (29·3)	
Sex ratio (F : M)	180 : 194	98 : 117	0·551
High co-morbidity burden (ADG ≥ 10)	185 (49·5)	104 (48·4)	0·798
Socioeconomic status (quintile)			0·816
1st (lowest)	54 (14·4)	27 (12·6)	
2nd	78 (20·9)	49 (22·8)	
3rd	74 (19·8)	45 (20·9)	
4th	85 (22·7)	42 (19·5)	
5th (highest)	83 (22·2)	52 (24·2)	
Rural living	42 (11·2)	29 (13·5)	0·545
Year of surgery			0·585
2004–2010	207 (55·3)	114 (53·0)	
2011–2015	167 (44·7)	101 (47·0)	

Values in parentheses are percentages. ADG, Aggregated Diagnosis Groups. *χ^2 test.

Statistical significance was set at $P \leq 0{\cdot}05$, using two-tailed testing. All analyses were conducted using SAS® Enterprise Guide 6.1 (SAS Institute, Cary, North Carolina, USA).

Results

Of 13 922 patients with pancreatic adenocarcinoma diagnosed over the study period, 1648 underwent pancreatectomy. Of those, 602 received adjuvant therapy. After excluding 13 patients who did not have surgery in a designated HPB centre, 589 patients were included in the study. Adjuvant therapy was delivered at the same institution as surgery for 374 patients (63·5 per cent). The characteristics of the included patients are detailed in *Table 1*. There was no difference in age between those receiving chemotherapy at the same institution as surgery or at a different institution (mean age of 62·5 and 63·8 years respectively). The two groups did not differ significantly in terms of co-morbidity burden, SES, rural residence or time period of surgery.

Pancreatoduodenectomy was the most commonly performed operation (*Fig. 1*). Histopathology characteristics are depicted in *Fig. 2*. The majority of patients had T3 disease, N1 nodal status and negative transection margins. There were no statistically significant differences between groups with respect to stage and margin positivity. There was no difference in the median number of chemotherapy cycles received between the groups, with 9 (i.q.r. 7–10) for the same institution as surgery *versus* 9 (6–11) for a different institution ($P = 0{\cdot}961$).

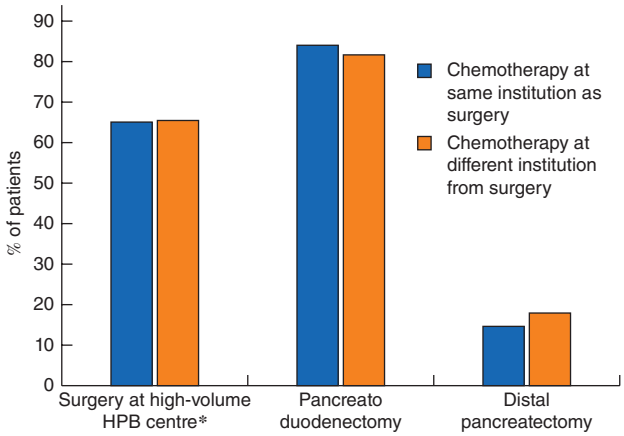

Fig. 1 Surgical therapy characteristics stratified by adjuvant chemotherapy institution
Frequency of adjuvant chemotherapy administration at the same institution as surgery or a different institution, according to the surgical procedure performed for the management of pancreatic adenocarcinoma. HPB, hepatopancreatobiliary. *$P = 0{\cdot}933$ (χ^2 test); $P = 0{\cdot}458$, pancreatoduodenectomy *versus* distal pancreatectomy (χ^2 test)

With a median follow-up of 21·9 (i.q.r. 12·4–38·6) months for the entire cohort, median OS was 21·3 (12·8–37·5) months for patients receiving their adjuvant chemotherapy at the same institution as surgery compared with 23·5 (11·5–40·4) months for those treated at a different institution. There was no difference in OS between the groups ($P = 0{\cdot}595$) (*Fig. 3*). OS rates at 1, 3 and 5 years were 76·7 (95 per cent c.i. 71·0 to 79·7), 26·2 (21·8 to 30·7) and 16·8 (13·2 to 20·9) per cent for patients receiving

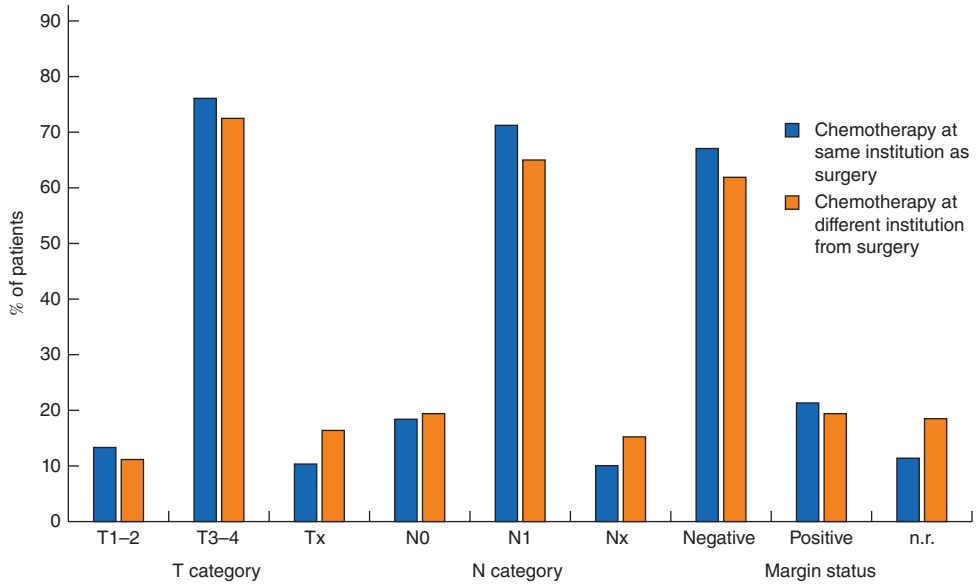

Fig. 2 Staging characteristics stratified by adjuvant chemotherapy institution
Frequency of adjuvant chemotherapy administration at the same institution as surgery or a different institution, according to tumour, node and margin status following resection of pancreatic adenocarcinoma. T category: $P = 0{\cdot}113$; N category: $P = 0{\cdot}142$; margin status $P = 0{\cdot}058$ (χ^2 test)

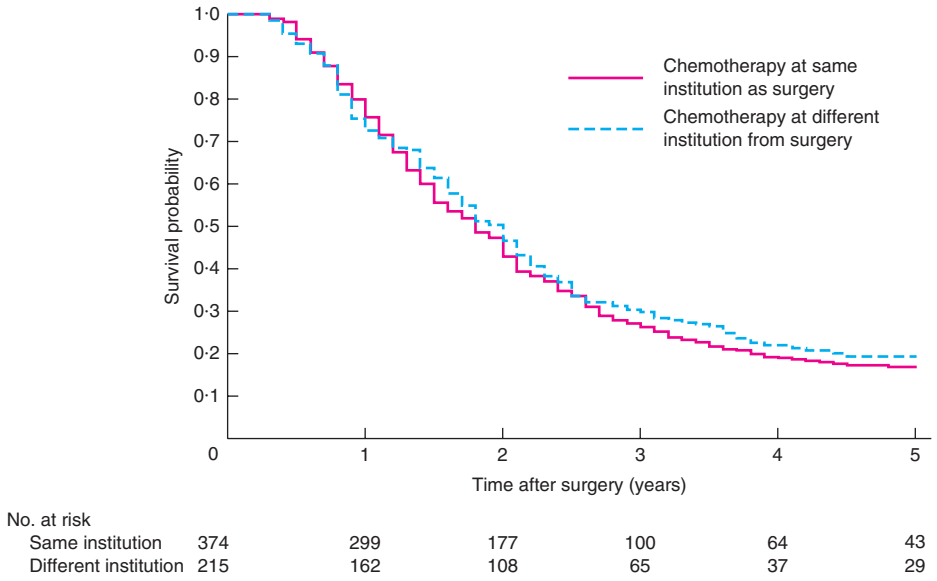

Fig. 3 Overall survival stratified by adjuvant chemotherapy institution
Probability of survival following surgery for pancreatic adenocarcinoma in patients who received adjuvant chemotherapy at the same institution as surgery or a different institution. $P = 0{\cdot}595$ (log rank test)

chemotherapy at the same institution as surgery, compared with 72·6 (66·1 to 78·0), 29·8 (23·8 to 35·9) and 19·3 (14·2 to 25·1) per cent respectively for those treated at a different institution from surgery. In multivariable analysis, after adjustment for age, sex, co-morbidity burden, SES, rural residence, T and N category, margin status and time period of surgery, receiving adjuvant chemotherapy at the same institution as surgery was not independently associated with OS (hazard ratio 1·03, 95 per cent c.i. 0·85 to 1·24). The factors independently associated with OS following

Table 2 Multivariable Cox regression analysis of the association between location of adjuvant chemotherapy and overall survival

	Hazard ratio	
	Univariable analysis	Multivariable analysis
Adjuvant chemotherapy at same institution as surgery	1·05 (0·88, 1·26)	1·03 (0·85, 1·24)
Age group (years)		
≤ 60	1·00 (reference)	1·00 (reference)
61–70	1·18 (0·96, 1·45)	1·18 (0·95, 1·46)
≥ 71	1·07 (0·85, 1·35)	1·11 (0·87, 1·41)
Sex		
F	1·00 (reference)	1·00 (reference)
M	0·93 (0·78, 1·11)	0·98 (0·81, 1·18)
High co-morbidity burden (ADG ≥ 10)	1·03 (0·87, 1·23)	1·04 (0·86, 1·24)
Socioeconomic status (quintile)		
1st (lowest)	1·00 (reference)	1·00 (reference)
2nd	1·22 (0·90, 1·64)	1·23 (0·91, 1·66)
3rd	1·04 (0·77, 1·41)	1·08 (0·79, 1·47)
4th	1·02 (0·75, 1·38)	1·02 (0·75, 1·38)
5th (highest)	0·85 (0·63, 1·15)	0·84 (0·62, 1·13)
Rural living	1·03 (0·79, 1·35)	0·99 (0·75, 1·31)
T category		
T1–2	1·00 (reference)	1·00 (reference)
T3–4	1·72 (1·29, 2·31)	1·59 (1·18, 2·14)
Missing	1·88 (1·30, 2·71)	1·15 (0·38, 3·49)
N status		
Negative	1·00 (reference)	1·00 (reference)
Positive	1·82 (1·43, 2·33)	1·76 (1·36, 2·27)
Missing	1·92 (1·37, 2·69)	2·50 (0·73, 8·57)
Transection margins		
Negative	1·00 (reference)	1·00 (reference)
Positive	1·69 (1·36, 2·09)	1·62 (1·30, 2·02)
Missing	1·32 (1·02, 1·71)	0·97 (0·54, 1·75)
Year of surgery		
2004–2010	1·00 (reference)	1·00 (reference)
2011–2015	0·82 (0·69, 0·99)	0·83 (0·68, 1·00)

Values in parentheses are 95 per cent confidence intervals. ADG, Aggregated Diagnosis Groups.

resection and adjuvant chemotherapy were T3–4 tumour, node-positive disease and a positive resection margin (*Table 2*).

Median time from surgery to delivery of chemotherapy did not differ between the groups: 70 (i.q.r. 58–85) and 69 (57–84) days for same *versus* different institution ($P = 0·512$). Patients who received chemotherapy at a different institution from that in which surgery was performed lived further away from the surgery centre (mean 106·7 km) than those who stayed at the same institution (44·7 km) ($P < 0·001$). Patients in both groups received adjuvant treatment at a similar distance from their residence. There was no difference in the mean distance between residence and location of chemotherapy delivery (26·5 and 22·9 km respectively for same and different institution groups; $P = 0·361$).

Discussion

In this population-based study, OS following curative intent resection for pancreatic adenocarcinoma was not affected by adjuvant chemotherapy being provided at the same institution where surgery had been performed or a different institution. Adjusting for demographic and clinical co-variables further confirmed the lack of association between the location of adjuvant chemotherapy treatment and OS. Receipt of chemotherapy at a different institution than the HPB centre of excellence allowed for shorter journey distances during this phase of care.

Adjuvant therapy is an important component of management with curative intent for pancreatic cancer, as evident from the CONKO-001 and ESPAC-4 trials[5,6,39]. Systemic therapy for pancreatic adenocarcinoma has progressed. Effective regimens are now available for metastatic disease and are being tested in the adjuvant setting[40,41]. Use of adjuvant therapy has increased over the past decades and, pending the results of adjuvant trials, may become even more important[38]. Recently, early report[42] of the PA.6 trial revealed an unprecedented improvement in OS for patients with pancreatic adenocarcinoma treated with adjuvant-modified FOLFIRINOX compared with gemcitabine. Providing outcomes are not affected, it is

important to facilitate access to chemotherapy for patients living away from specialized cancer centres[43–45].

Although there is a large body of evidence regarding the volume–outcome relationship for pancreatic surgery, there are no data examining the impact of where adjuvant chemotherapy is received on survival[9,46]. For uterine cancer, it has been reported[17] that 50 per cent of women receive a combination of care at different institutions, with 25 per cent of patients referred from community centres to specialized centres for surgical care followed by a return to their local institution for the adjuvant chemotherapy phase of treatment. Receipt of adjuvant therapy at lower-volume local institutions was associated with a trend towards a greater likelihood of mortality from chemotherapy (relative risk 1·95, 95 per cent c.i. 1·24 to 3·08), but long-term outcomes were not assessed. A single-institution experience on this issue for pancreatic adenocarcinoma was communicated in abstract form to the American Society of Clinical Oncology Annual Meeting[47]; inferior OS was described in patients who had surgery at the authors' centre but then received adjuvant chemotherapy in community institutions, compared with that in patients who received both surgery and adjuvant chemotherapy at their institution. The single-institution design may be important here; a factor that also hampers generalizability.

HPB surgical care in the province of Ontario has been regionalized to ten designated centres of excellence, with resultant decreased perioperative mortality from 10·4 per cent to less than 2·2 per cent[10]. This means that patients often must travel long distances to have surgery, which can be burdensome to both patients and providers[48].

Travel distance can represent an important barrier to access to medical care. Indeed, distance to medical care has been reported to be inversely related to the use of healthcare resources. The ability to overcome long travel distances to access care is compounded by multiple factors such as lower SES or increased transportation difficulties among those in rural areas[49,50]. In the USA, patients living in rural areas travel double the distance for medical services compared with those from non-rural areas (28·2 *versus* 13·4 km)[49]. Previous work[48,51] in pancreatic and colonic cancer revealed that the need to travel long distances to receive surgery at high-volume centres was associated with lower odds of receiving adjuvant therapy.

In the present population-based analysis, nearly 40 per cent of patients received chemotherapy closer to home at a different institution from where they had undergone surgery.

Investigations into patient preferences have revealed that patients with cancer are willing to travel to access specialized surgical care and improve their outcome[15]. However, if there is no increased risk of complications or death, patients prefer to be cared for locally, closer to home, as this often allows for reduced patient-incurred costs and increased social support from family and friends[16]. In the present study, patients who received adjuvant treatment at a different institution from that where they had surgery travelled a mean of 83·8 km more to undergo pancreatic resection, but no extra distance to receive chemotherapy (26·2 and 22·9 km for the 2 chemotherapy groups). Combined with lack of difference in baseline characteristics between the groups, this indicates that the institution where adjuvant therapy was received was probably dictated by geography, providing patients part of their care closer to home when available. The study highlights the ability to obtain similar survival for patients by combining surgery for pancreatic adenocarcinoma in specialized centres with decentralized administration of adjuvant chemotherapy, closer to home. This is crucial information for designing patient-centred and sustainable healthcare delivery strategies and networks of cancer care that support patients to be cared for close to their homes while being offered optimal cancer outcome, along with better social support, enhanced experience and reduced travelling and financial burdens[15,16,49,50].

This study has a number of limitations associated with the study design and use of administrative data. It was conducted in the context of a single-payer, universal healthcare system. Although this has the benefit of capturing all healthcare information through administrative data for a comprehensive analysis, it may differ from other healthcare systems. However, the analysis focused on potential disparities in outcomes due to organization of care, and the challenges associated with receipt of care over multiple institutions and long travelling distances for patients. The study specifically selected patients who received adjuvant chemotherapy – a fraction of the total surgical pancreatic adenocarcinoma population. Variability in the use of adjuvant chemotherapy between HPB centres of excellence and local community health centres may also exist, and have an impact on outcomes. Examination of disparities and barriers to receipt of chemotherapy or other treatments was beyond the scope of this analysis.

This study has shown that a large cohort of patients with pancreatic adenocarcinoma can be treated at disparate institutions without detriment to survival. It included granular pathology data through a validated provincial chart review, thereby addressing one of the traditional limitations of studies using administrative healthcare data sets. This type of study may be more reflective of outcome in a healthcare system as a whole compared with studies performed at a single institution or a selected group of institutions.

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