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Economic Analysis of Adjuvant Chemoradiotherapy Compared with Chemotherapy in Resected Pancreas Cancer

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ABSTRACT

Background. Population-based survival and costs of pancreas adenocarcinoma patients receiving adjuvant chemoradiation and chemotherapy following pancreaticoduodenectomy are poorly understood.

Methods. This retrospective cohort study used linked administrative and pathological datasets to identify all patients diagnosed with pancreas adenocarcinoma and undergoing pancreaticoduodenectomy in Ontario between April 2004 and March 2014, who received postoperative chemoradiation or chemotherapy. Stage and margin status were defined by using pathology reports. Kaplan–Meier and Cox proportional hazards regression survival analyses were used to determine associations between adjuvant treatment approach and survival, while stratifying by margin status. Median overall health system costs were calculated at 1 and 3 years for chemoradiation and chemotherapy, and differences were tested using the Kruskal–Wallis test.

Results. Among 709 patients undergoing pancreaticoduodenectomy for pancreas cancer during the study period, the median survival was 21 months. Median survival was 19 months for chemoradiation and 22 months for chemotherapy. Patients receiving chemoradiation were more likely to have positive margins: 47.7% compared with 19.2% in chemotherapy. After stratifying by margin status and controlling for confounders, adjusted hazard ratio of death were not statistically different between chemotherapy and chemoradiation [margin positive, hazard ratio (HR) = 0.99, 95% confidence interval (CI) = 0.88–1.27; margin negative, HR 0.95, 95% CI 0.91–1.18]. Overall 1-year health system costs were significantly higher for chemoradiation (USD $70,047) than chemotherapy (USD $54,005) ($p \leq 0.001$).

Conclusions. Chemotherapy and chemoradiation yielded similar survival, but chemoradiation resulted in higher costs. To create more sustainable healthcare systems, both the efficacy and costs of therapies should be considered.

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Pancreas cancer (PC) is a lethal diagnosis worldwide. In 2018 alone, it is estimated that 55,400 adults were diagnosed with PC in the United States, and 44,300 died as a

result of the disease.[1] Five-year overall survival in PC patients is extremely low at 8% compared with 64% for colorectal cancer patients. The only curative option for these patients is surgical resection of the tumor.[2]

To improve survival following surgery, clinical guidelines recommend adjuvant therapy, such as chemotherapy (CT) and chemoradiotherapy (CRT). However, the optimal adjuvant treatment approach remains controversial as there is conflicting evidence. Supporting CRT, the Gastrointestinal Tumor Study Group (GITSG) showed a doubling of median survival for patients undergoing CRT compared with patients receiving surgery alone. In contrast, the European Study Group for Pancreatic Cancer (ESPAC-1) trial showed worse 5-year survival in patients receiving CRT compared with CT.[3,4] Outside the rigorous environment of randomized control trials, few cohort studies have examined CRT compared with CT in the adjuvant setting. A recent population-based analysis in Ontario, Canada's most populous province, demonstrated no difference in survival between patients receiving CT and CRT, with an adjusted hazard ratio of 0.98 [95% confidence interval (CI) 0.74, 1.31]. However, this study was unable to adjust for margin status, an important predictor of survival.[5] This inconsistency in evidence has resulted in variability in clinical treatment guidelines for PC. The European Society for Medical Oncology recommends treatment with adjuvant CT and *against* CRT in PC patients.[6] Similarly, Cancer Care Ontario recommends adjuvant CT and states that CRT requires further study.[7] In contrast, the National Comprehensive Cancer Network guidelines recommend adjuvant CT or CRT.[8]

Considering the discrepancy in recommendations for CT and CRT, and to improve sustainability of health care systems, it is important to consider the costs of these treatments to the healthcare system, particularly because PC is one of the most expensive cancers to treat.[9] Not only does the addition of radiotherapy contribute to greater health system costs, but patients may experience complications when treated with either CT or CRT. These complications have the potential to significantly impact quality of life, as well as increase the use of healthcare resources and the cumulative costs of PC treatment. Understanding the cost-effectiveness of cancer treatments and why variation in costly management strategies exist allows for intervention and potential reduction in the economic burden of care.

Therefore, we conducted a retrospective, population-based cohort study, using real-world health system administrative data, to compare overall survival between PC patients receiving adjuvant CT and CRT after pancreaticoduodenectomy and calculated healthcare costs incurred by a single-payer system, according to adjuvant therapy approach.

MATERIALS AND METHODS

Study Design and Population

We conducted a retrospective, cohort study to examine survival and healthcare costs in patients undergoing adjuvant therapy after curative-intent pancreaticoduodenectomy for pancreas adenocarcinoma in the province of Ontario, Canada, which has a population of 14.2 million. Patients were diagnosed from April 1, 2004 to March 1, 2014, with follow-up until March 1, 2017, allowing for a minimum of 3 years follow-up for all patients. Patients diagnosed with PC were identified using the Ontario Cancer Registry (OCR), which captures approximately 95% of incident cancer cases in the province.[10] Topography and histology codes from the World Health Organization International Classification of Diseases for Oncology, 3rd edition, were used to define PC (Table 5).

Patients undergoing pancreaticoduodenectomy were identified for inclusion using procedure codes from the Canadian Classification of Health Interventions (CCI) (Table 5). Patients were excluded if they were younger than age 18 years, had any other diagnosis of cancer at any time, received neoadjuvant chemotherapy or radiotherapy, did not receive CT or CRT following surgery, or if they underwent distal pancreatectomy, enucleation, or total pancreatectomy.

Data Sources

Ontario's single-payer healthcare system captures all publicly funded healthcare encounters for its residents in centralized, administrative databases. These data are linked using unique encoded identifiers at ICES.

Data were obtained from the following databases: (1) OCR; (2) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), includes diagnostic and discharge data for all hospital admissions; (3) Registered Persons Database (RPDB), includes demographic information (including date of death) for all Ontario residents eligible for care under the Ontario Health Insurance Plan (OHIP); (4) OHIP Database, includes all physician claims data for insured healthcare services provided under OHIP; (5) Cancer Activity Level Reporting Database (ALR), includes patient-level information on consultations and treatment provided at Ontario's Regional Cancer Centres, including receipt of radiotherapy; (6) National Ambulatory Care Reporting System (NACRS), contains data for all hospital-based and community-based ambulatory visits; (7) New Drug Funding Program (NDFP) database, includes publicly funded new and expensive antineoplastic and injectables; (8) Ontario Drug Benefit (ODB)

database, includes drugs received under public insurance for residents aged 65 years or older or those with low income, or disabilities; and (9) the Pancreas Cancer Pathology database, which includes abstracted pathology reports of operative specimens acquired from the Ontario Cancer Registry.[5]

Ethics approval for this study was obtained from the Sunnybrook Health Sciences Centre Research Ethics Board. We adhered to the data confidentiality and privacy policies of ICES.

Treatment

Adjuvant therapy was categorized as CT or CRT based on OHIP billing codes and ALR activity. Patients with two or more records for radiation in the ALR, within 180 days of pancreaticoduodenectomy, were defined as receiving CRT. CRT patients were assumed to have also received chemotherapy, as radiation alone is not standard of care for patients receiving pancreaticoduodenectomy for pancreas adenocarcinoma. Patients with two or more billing codes for chemotherapy in OHIP and fewer than two records of radiation during the same time period were included in the CT group (Table 6). The time frame of 180 days following surgery was chosen to identify curative-intent adjuvant treatment. Patients in the CT group may have received radiation after 180 days following surgery; however, this was not considered to be of curative intent.

Outcomes

Survival Overall survival was defined using date of death from any cause in the RPDB and measured from the date of surgery. Three-year survival was presented using Kaplan–Meier curves stratified by margin and node status, which were used to calculate median overall survival.

Cost General health care, chemotherapy, and radiation costs were assessed from the perspective of the healthcare system using methodologies developed at ICES: Person-Level Case-Costing Methodology, Cancer Medication Costing Methodology, and Cancer Radiation Therapy Costing Methodology.[11–13] Median costs were calculated per patient over 1- and 3-year time periods and presented in 2018 U.S. dollars. A conversion of 1 Canadian dollar to 0.77 U.S. dollars was applied, as per the Bank of Canada's rate in September 2018. We analyzed median costs to avoid skewing the measure of central tendency with outliers. We did not calculate cost per month lived, because survival was similar between groups.

General Healthcare Costs The Person-Level Case-Costing Methodology developed at ICES was used to estimate patient-level costs, including inpatient hospitalization, inpatient rehabilitation, emergency department care, outpatient and clinic visits, physician billings, complex continuing care and long-term care, home care services, admissions to mental health beds, and the assisted device program.[11] Total costs of encounters for hospital-based costs were calculated by multiplying resource intensity weights (RIW) by annual cost-per-weighted-case to determine annual cost-per-weighted-case. RIWs are annual ratios that represent expected resource consumption for average patients within specific patient demographics and diagnoses.[14] For longer-term care resources, costs were determined by weighted days.

Radiation Therapy Costing Radiation costs were assessed using the Cancer Radiation Therapy Costing Methodology developed by Mittmann et al.[13] Costs were calculated for treatment (cancer clinic costs, physician reimbursement, and radiation therapist), planning (physician reimbursement and radiation therapist), and operational (physician reimbursement and radiation therapist activity). The per-visit cost of equipment and supplies and medical physicist was determined and included in the cost.

Chemotherapy Costing Cost of chemotherapy drugs were assessed by using the Cancer Medication Costing Methodology developed by Mittmann et al.[13] Data on chemotherapy drug utilization were obtained from three sources: (1) ODB program for prescription drugs dispensed in the community for ODB-eligible patients (e.g., social assistance and > 64 years); (2) NDFP for in-hospital administration of new, and often expensive chemotherapy drugs; and (3) ALR for in-hospital administration of all standard chemotherapy and supportive drugs. These data sources overlap in coverage; however, only one record per drug per day was used for our analysis. We defined the following drugs as chemotherapeutic agents: capecitibine, cisplatin, 5-fluorouracil, gemcitabine, irinotecan, leucovorin, nabpaclitaxel, oxaliplatin. If more than one agent was administered on a given day, we assumed the agents were given as combination therapy; however, combination therapies may be underestimated, because we were not able to capture privately insured oral chemotherapies, including capecitabine. We created an algorithm to calculate chair time cost using infusion duration guidelines from the Cancer Care Ontario regimen monograph.[15] Infusion duration times were specified for each chemotherapy regimen and were multiplied by an hourly chemotherapy infusion cost described in the literature.[16]

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Covariates

Baseline demographics were measured at the time of surgery. Age ($\leq$ 54, 55–64, 65–74, and $\geq$ 75 years) and sex were obtained from the RPDB. Comorbidity burden was defined using the Johns Hopkins-Adjusted Clinical Groups (ACG) system.[17,18] Comorbidity score was defined by summing the number of ACG Aggregated Diagnosis Groups (ADGs) and dichotomized (0–9 vs. $\geq$ 10). Neighborhood income quintiles were defined according to the median community income and obtained from national census data. Receipt of treatment at a high-volume centre was based on the surgery being performed at one of ten provincially designated hepatopancreaticobiliary centres compared with any other centre.[19] Tumor histopathologic characteristics were abstracted from pathology reports. The following characteristics were used as covariates: T stage (Tis/missing, T1–2, T2–3), N stage (negative, positive, missing/not reported), margin status (negative, positive, missing/not reported), tumor grade (well/moderately differentiated, poorly/undifferentiated, missing/not reported), lymphovascular invasion (no, yes, missing/not reported), and perineural invasion (no, yes, missing/not reported).[5] In multivariable analyses, missing categories were combined with negative categories for node and margin status due to a large number of missing reports.

Statistical Analysis

Baseline characteristics of the study cohort were summarized using descriptive statistics. Differences between the CT and CRT groups were compared using Chi square tests. Survival comparisons between CT and CRT groups were stratified by margin status because this is used as an indication for adjuvant treatment in clinical practice and therefore was considered an effect modifier.[7] We used Kaplan–Meier survival analyses and Multivariable Cox proportional hazards regression to determine associations between the adjuvant approaches and survival. Kaplan–Meier curves were additionally stratified by node status. Based on clinical significance, covariates were identified a priori as age, sex, comorbidity, undergoing surgery at a provincial hepatopancreaticobiliary center, nodal status, T stage, perineural invasion, and tumor grade. One-year and 3-year costs were assessed for both treatment groups using medians and interquartile ranges (IQR), and statistical differences were determined using Kruskal–Wallis tests. All analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute, Cary, NC). Results were considered statistically significant if $p < 0.05$.

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RESULTS

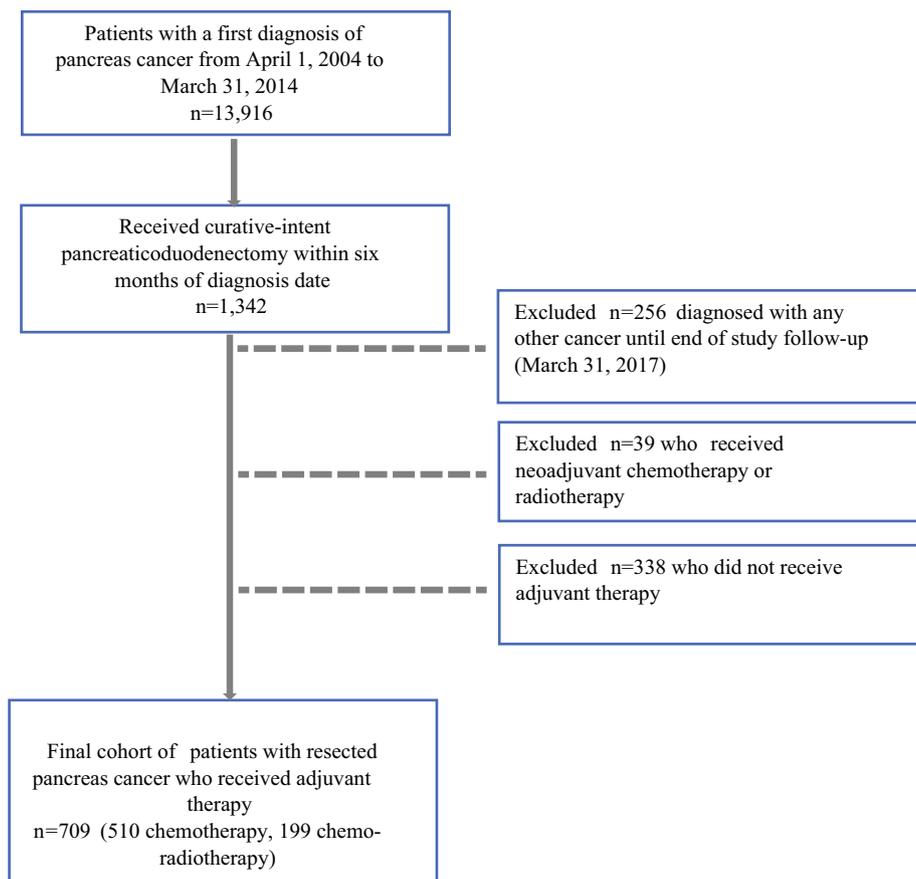*Population Description and Demographics*

A total of 1342 patients were diagnosed with PC and underwent pancreaticoduodenectomy between April 1, 2004 and March 31, 2014. Following exclusions, the final cohort consisted of 709 patients; 510 received CT and 199 received CRT (Fig. 1). Except for 13 patients, all patients in the CRT group also received chemotherapy. Those 13 patients remained in the CRT group, because they may have received oral chemotherapy not captured in the administrative databases. Demographic and pathologic characteristics between CT and CRT were similar, with the exception of margin status. CRT patients were more likely to have positive margins compared with CT patients (47.7% vs. 19.2%; Table 1).

Survival

Median overall survival for the entire cohort was 21 months [interquartile range (IQR) 12–36]. Survival for CT was 22 months (IQR 12–37) and 19 months (IQR 12–36) for CRT. Kaplan–Meier 3-year survival analyses showed no difference between CT and CRT after stratifying by node and margin status (log rank = 0.411; Fig. 2). On multivariable analyses stratified by margin status, treatment was not statistically significantly associated with survival [CRT vs. CT margin-positive hazard ratio (HR) 0.88 (95% confidence interval (CI) 0.61–1.27); margin-negative HR 0.91 (95% CI 0.69–1.18); Table 2].

Treatment Received and Costs

Patients in both CT and CRT groups were most likely to receive gemcitabine regimens (83% in CT and 52% in CRT). The second most common treatment in the CRT group was 5FU (34%), whereas patients in the CT group were more likely to receive intravenous combination therapies (Table 3). Patients in the CRT group received a median of 25 fractions of radiotherapy (IQR 25–28 fractions) and 30 days on chemotherapy (IQR 23–39). Patients in the CT group received a median of 22 days on chemotherapy (IQR 16–29). Median total costs differed between CT and CRT patients, with total 1-year median costs $54,005 (IQR $43,091–$69,271) for CT and $70,047 (IQR $56,414–85,385) for CRT ($p < 0.001$; Table 4). Although patients in the CT group received fewer days of administered chemotherapy, they had slightly higher costs for chemotherapy provision compared to patients in the CRT group (median of $4926 vs. $3882, $p = 0.002$), indicating more expensive regimens. Not surprisingly, patients in the CRT group had higher costs for radiotherapy

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FIG. 1 Stepwise exclusion of patients for final cohort creation

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┌─────────────────────────────────┐
│ Patients with a first diagnosis of │
│ pancreas cancer from April 1, 2004 to │
│         March 31, 2014          │
│           n=13,916              │
└─────────────────────────────────┘
                 │
┌─────────────────────────────────┐
│    Received curative-intent     │
│ pancreaticoduodenectomy within six │
│      months of diagnosis date   │
│           n=1,342               │
└─────────────────────────────────┘
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┌──┐
│ Excluded n=256 diagnosed with any other cancer until end of study follow-up (March 31, 2017) │
└──┘

┌──┐
│ Excluded n=39 who received neoadjuvant chemotherapy or radiotherapy │
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┌──┐
│ Excluded n=338 who did not receive adjuvant therapy │
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┌─────────────────────────────────┐
│ Final cohort of patients with resected │
│ pancreas cancer who received adjuvant │
│           therapy               │
│ n=709 (510 chemotherapy, 199 chemo- │
│         radiotherapy)           │
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compared with patients in the CT group (median of $14,238 vs. $0, $p < 0.001$). Some patients in the CT group still incurred radiotherapy costs ($216 1-year cost and $435 3-year cost for the 75th percentile), which may be due to noncurative intent radiation, or radiation oncologist consultation and planning, but no actual provision of radiation (Table 4; Supplemental Table 1). There were no statistically significant differences for 1-year general healthcare costs between CT and CRT (median of $47,382 for CT vs. $49,882 for CRT, $p = 0.29$).

Three-year median total costs reflected a similar pattern as 1-year costs, with $71,374 (IQR $52,933–98,296) for CT compared with $87,931 (IQR $70,250–110,524) for CRT ($p < 0.001$; Supplemental Table 1).

DISCUSSION

This is the first population-based, retrospective analysis to examine survival and costs of CRT compared to CT in resected PC. We demonstrated no real-world survival benefit of receiving CRT compared with CT among PC patients following resection, in an analysis stratified for margin status. Furthermore, the costs incurred by the

healthcare system through administering CRT are significant, with CRT costing 22.5% more compared with CT alone.

Many studies to date examine the survival benefits of CRT compared with surgery alone, indicating a significant benefit for CRT.[20–22] However, these conclusions do not incorporate the benefits of receiving only CT compared with CRT, and few studies have examined adjuvant survival benefits of CRT to CT.[3,5] We created a large, population-based cohort of resected PC patients and did not identify any survival benefits of using CRT over CT. Survival results in our analysis are consistent with published results from RCTs.[3,19,20,22]

Differences in costs between CT and CRT are attributed mostly to the additional cost of radiotherapy, costing an additional median of $16,042 per year per patient in the first year following diagnosis. The American Cancer Society's estimates that 55,440 new cases of PC were diagnosed in 2018, and approximately 8870 of those patients would have undergone surgical resection, based on a resection rate of 16%.[1,23] Although the rate of adjuvant CRT in our Ontario study was 19%, and a recent analysis of six European countries the rate was only 4.1%, studies show that approximately 30% of patients receive adjuvant

TABLE 1 Baseline characteristics of patients receiving either CT or CRT following curative-intent pancreaticoduodenectomy for pancreas cancer (n = 709)

Variable	Category	CT (n = 510)	CRT (n = 199)	p value*
Age group (years)	≤ 54	100 (19.6%)	43 (21.6%)	0.651
	55–64	168 (32.9%)	59 (29.6%)	
	65–74	173 (33.9%)	74 (37.2%)	
	≥ 75	69 (13.5%)	23 (11.6%)	
Sex	F	228 (44.7%)	90 (45.2%)	0.900
Aggregated diagnosis groups (comorbidity)	≥ 10	259 (50.8%)	85 (42.7%)	0.053
Neighborhood income	1	61 (12.0%)	27 (13.6%)	0.146
(missing in one CRT patient)	2	97 (19.0%)	40 (20.1%)	
	3	86 (16.9%)	30 (15.1%)	
	4	94 (18.4%)	29 (14.6%)	
	5	112 (22.0%)	35 (17.6%)	
	Rural	59 (11.6%)	38 (19.1%)	
Treatment at high volume center	Yes	322 (63.1%)	129 (64.8%)	0.675
Node	Negative	78 (15.3%)	28 (14.1%)	0.375
	Positive	363 (71.2%)	151 (75.9%)	
	Missing	69 (13.5%)	20 (10.1%)	
Margin	Negative	333 (65.3%)	83 (41.7%)	**< 0.001**
	Positive	98 (19.2%)	95 (47.7%)	
	Missing	79 (15.5%)	21 (10.6%)	
T stage	Tis/missing	70 (13.7%)	21 (10.6%)	0.505
	T1/T2	58 (11.4%)	22 (11.1%)	
	T3/T4	382 (74.9%)	156 (78.4%)	
Perineural invasion	No	33 (6.5%)	14 (7.0%)	0.087
	Yes/indeterminate	377 (73.9%)	160 (80.4%)	
	Missing	100 (19.6%)	25 (12.6%)	
Lymphovascular invasion	No	110 (21.6%)	57 (28.6%)	**0.040**
	Yes/indeterminate	294 (57.6%)	114 (57.3%)	
	Missing	106 (20.8%)	28 (14.1%)	
Tumor grade	Well/moderately differentiated	362 (71.0%)	140 (70.4%)	0.302
	Poorly/undifferentiated	78 (15.3%)	38 (19.1%)	
	Missing	70 (13.7%)	21 (10.6%)	

*p values were calculated using Chi square tests; $p < 0.05$ were considered significant and are presented in bold

CRT in the United States.[23,24] This corresponds to approximately 2600 patients receiving adjuvant CRT in 2018 in the United States. Based on the results of our costing analysis, this represents an additional expenditure of $41,700,000. Although the use of adjuvant CRT after PC resection is trending downwards, the number of patients receiving CRT is still high, especially given the significant cost.[24] With the publication of the recent PRODIGE (Partenariat de Recherche en Oncologie Digestive) 24-ACCORD (Actions Concertées dans les Cancers Colorectaux et Digestifs) 24/CCTG PA-6 (Canadian Cancer Trials Group Pancreatic Adenocarcinoma) study, showing superior results for FOLFIRINOX in the adjuvant setting, the utilization of CRT as adjuvant therapy should be reconsidered.[25]

Implications and Future Directions

Although the effectiveness of CRT has been in question for some time, it has been the standard of care for PC patients receiving curative resection in the United States.[20] Given the lack of survival benefits and associated costs, it is difficult to justify the routine use of adjuvant CRT for resected PC. Ongoing trials (PRODIGE 24-ACCORD 24/CCTG PA 6, APACT, and ESPAC-4) investigating the role of adjuvant FOLFIRINOX and gemcitabine/nab-
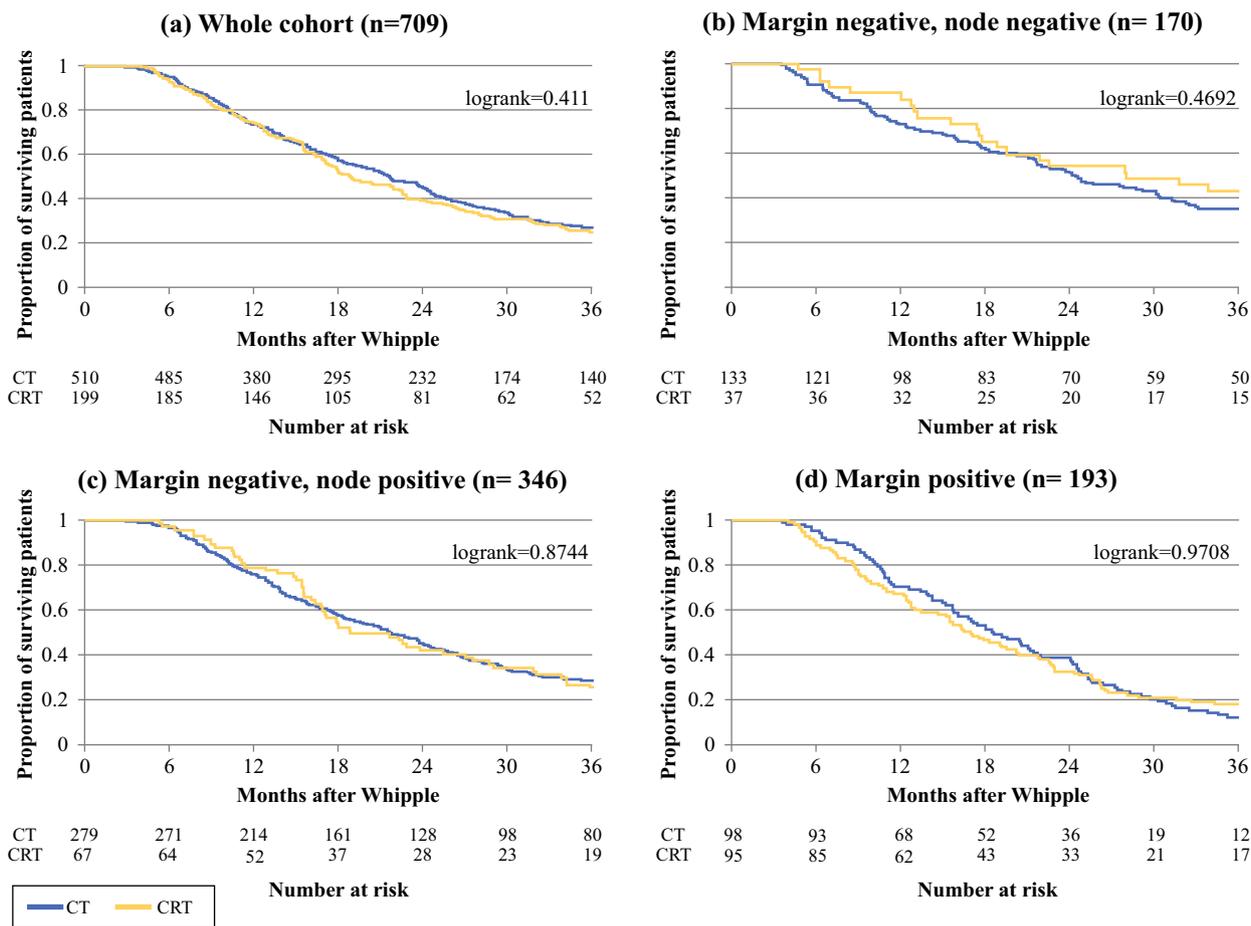
(a) Whole cohort (n=709)

logrank=0.411

CT	510	485	380	295	232	174	140
CRT	199	185	146	105	81	62	52

Number at risk

(b) Margin negative, node negative (n= 170)

logrank=0.4692

CT	133	121	98	83	70	59	50
CRT	37	36	32	25	20	17	15

Number at risk

(c) Margin negative, node positive (n= 346)

logrank=0.8744

CT	279	271	214	161	128	98	80
CRT	67	64	52	37	28	23	19

Number at risk

(d) Margin positive (n= 193)

logrank=0.9708

CT	98	93	68	52	36	19	12
CRT	95	85	62	43	33	21	17

Number at risk

CT CRT

FIG. 2 Kaplan–Meier curves of 3-year survival in patients receiving adjuvant therapy after pancreaticoduodenectomy for pancreas cancer, stratified by margin and node status

TABLE 2 Multivariable* Cox proportional hazards model identifying association between CT and CRT and survival, stratified by margin status

Category	Univariate hazard ratio	Adjusted hazard ratio	Lower 95% CI	Upper 95% CI	p value
Margin positive					
Chemotherapy	1.00	1.0			
Chemoradiation	0.99	0.88	0.61	1.27	0.501
Margin negative					
Chemotherapy	1.00	1.00			
Chemoradiation	0.95	0.91	0.69	1.18	0.465

CI confidence interval

*Adjusted for: age, sex, comorbidity, high volume center, nodal status, T stage, perineural invasion and tumor grade

paclitaxel as well as capecitabine plus gemcitabine compared with gemcitabine alone, should prompt reexamination of guidelines for adjuvant therapy options, including the utility of CRT in margin negative patients.[26] Survival, as well as costs, associated with these aggressive therapeutic agents in both the adjuvant and neoadjuvant setting should be considered to improve sustainability of healthcare systems. Patients also experience out-of-pocket costs associated with additional treatments. For example, patients receiving radiotherapy must make frequent visits to the hospital, which may involve paying for parking and/or transit, taking time off work resulting in loss of pay, or arranging for family care.[27,28] In addition to out-of-pocket costs, patients who receive radiotherapy may experience

TABLE 3 Frequency of receipt of chemotherapy regimens among all patients

Drug regimen	Number of administrations, n (%)[a]	
	CT	CRT
Gemcitabine	5123 (83.1%)	1318 (51.8%)
5FU leucovorin combination therapy	736 (11.9%)	330 (13.0%)
5FU	37 (0.6%)	856 (33.7%)
FOLFIRINOX	147 (2.4%)	9 (0.4%)
Other	125 (2.0%)	30 (1.2%)

[a]If a chemotherapy regimen was recorded multiple times for a patient in 1 day, it was only counted as one administration

TABLE 4 Median healthcare costs in patients receiving adjuvant therapy after pancreaticoduodenectomy surgery for pancreas cancer, from date of surgery until 1 year after surgery. 2018 U.S. dollars

Cost component	CT Median $ (IQR)	CRT Median $ (IQR)	p value*
Radiotherapy costs			
Equipment and supplies	0 (0–0)	1816 (730–2128)	**< 0.001**
Medical physicist	0 (0–0)	962 (962–1077)	**< 0.001**
Therapy planning (including physician billing)	0 (0–110)	1195 (1079–1352)	**< 0.001**
Therapy delivery (including physician billing)	0 (0–117)	14,170 (11,127–21,131)	**< 0.001**
Alternate funding arrangement payments for radiation oncologist	0 (0–80)	178 (134–232)	**< 0.001**
Subtotal radiotherapy costs	0 (0–216)	14,238 (11,241–21,299)	**< 0.001**
Chemotherapy costs			
Chair time	3092 (825–3711)	2474 (1100–3092)	**0.005**
Chemotherapy drugs	2152 (770–3736)	1146 (487–2062)	**< 0.001**
Supportive drugs	145 (32–466)	228 (56–781)	**0.014**
Subtotal chemotherapy costs	4926 (1793–7511)	3882 (2312–5648)	**0.002**
Other healthcare costs			
Outpatient clinic	2204 (1003–3629)	2887 (1727–4485)	**< 0.001**
Emergency department	473 (0–947)	297 (0–895)	0.099
Dialysis	0 (0–0)	0 (0–0)	0.532
Cancer clinic, excluding radiotherapy	12,595 (5790–18,417)	11,974 (7047–16,916)	0.837
Inpatient stay	18,621 (13,704–27,982)	21,091 (13,544–31,468)	0.340
Rehabilitation	0 (0–0)	0 (0–0)	0.400
Complex continuing care	0 (0–0)	0 (0–0)	0.973
Long-term care	0 (0–0)	0 (0–0)	0.532
Home care services	2118 (744–4427)	2187 (903–4626)	0.505
Inpatient mental health	0 (0–0)	0 (0–0)	0.279
Physician billing, excluding radiotherapy	7235 (5752–9081)	6781 (5627–8666)	0.127
Subtotal general healthcare expenditures	47,382 (37,513–60,348)	49,882 (37,206–62,297)	0.290
Total cost			
Total healthcare spending	54,283 (43,720–69,851)	70,047 (57,462–85,513)	**< 0.001**

*p values were calculated using Kruskal–Wallis tests; $p < 0.05$ were considered significant and are presented in bold

higher complication rates or report more symptoms compared with those who receive chemotherapy alone.[26,29,30] In a disease with a relatively short survival and where symptom burden is already high, it is important to minimize any other negative consequences from treatment and improve overall patient quality of life. Therefore, these factors are especially important to consider and should be examined in future studies.

Limitations

Strengths of this study include the large population-based sample size, inclusion of histopathologic variables from surgical pathology reports, and the presentation of survival and costing results simultaneously for the same patients. However, this study has some limitations. This was an observational study using data from administrative healthcare databases, which may result in unmeasured confounding. For example, we were unable to control for physician characteristics that may impact the receipt of CT or CRT and survival. Next, patients who received CRT were more likely to have advanced disease, as evidenced through higher rates of positive margins in this group. This introduces selection bias, because patients in the CRT group may already have shorter survival length, regardless of treatment, resulting in a perceived minimization of the survival benefit of CRT treatment. We have accounted for this as best as possible with cohort stratification and multivariable modelling. We also may not have been able to capture all oral chemotherapy taken by patients younger than age 65 years who were ineligible for the ODB. This is important to consider given that 52% of the study cohort was younger than 65 years and may be particularly important when identifying combination therapy. For example, patients who received gemcitabine also may have received oral chemotherapy, which was not captured in the administrative databases. However, this potential under-costing is unlikely to change our final conclusions given that the cost of chemotherapy agents represents only 4.5% and 1.6% of the total healthcare costs of the CT and CRT groups, respectively.

CONCLUSIONS

This study provides some evidence against the use of CRT in resected PC. Cancer programs might consider revising their guidelines to discourage the use of adjuvant CRT for PC, based on the lack of evidence suggesting a clear survival benefit over CT and the high costs associated with CRT. There is an obvious need to focus efforts on improving systemic therapy options for PC and future research should delve into alternative methods to improve survival in this patient population.

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APPENDIX

See Tables 5 and 6.

TABLE 5 Defining patients with pancreas cancer who underwent pancreaticoduodenectomy

Case-finding criteria	Eligible codes
ICD-O-3 topography code	C25.0–C25.9
ICD-O-3 histology code	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
CCI procedure code	1.OK.87.^^, 1.OK.91.^^

ICD-O-3 international classification of diseases for oncology, 3rd edition; *CCI* Canadian classification of health interventions

TABLE 6 Codes for chemotherapy and radiotherapy

Therapy	Database	Codes
Chemotherapy	Ontario health insurance plan	G381, G281, G339, G345, G359
Radiotherapy	Cancer Care Ontario activity level reporting: national hospital productivity improvement project	120, 130, 503, 510, 511, 512, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 548, 549, 561, 563, 565, 566, 568, 570, 571, 572, 573, 574, 575, 581, 582, 590, 591, 592, 594, 596, 597

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