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Predictors of adjuvant treatment for pancreatic adenocarcinoma at the population level

D.J. Kagedan MD,* M.E. Dixon MD,† R.S. Raju MS,‡ Q. Li MMath,§ M. Elmi MD,* E. Shin,|| N. Liu MSc,§ A. El-Sedfy MD,# L. Paszat MD MS,‡§|| A. Kiss PhD,‡§** C.C. Earle MD MSc,‡§|| N. Mittmann PhD,†† and N.G. Coburn MD MPH*‡§||**

ABSTRACT

Background In the present study, we aimed to describe, at the population level, patterns of adjuvant treatment use after curative-intent resection for pancreatic adenocarcinoma (PCC) and to identify independent predictors of adjuvant treatment use.

Methods In this observational cohort study, patients undergoing PCC resection in the province of Ontario (population 13 million) during 2005–2010 were identified using the provincial cancer registry and were linked to administrative databases that include all treatments received and outcomes experienced in the province. Patients were defined as having received chemotherapy (CTX), chemoradiation (CRT), or observation (OBS). Clinicopathologic factors associated with the use of CTX, CRT, or OBS were identified by chi-square test. Logistic regression analyses were used to identify independent predictors of adjuvant treatment versus OBS, and CTX versus CRT.

Results Of the 397 patients included, 75.3% received adjuvant treatment (27.2% CRT, 48.1% CTX) and 24.7% received OBS. Within a single-payer health care system with universal coverage of costs for CTX and CRT, substantial variation by geographic region was observed. Although the likelihood of receiving adjuvant treatment increased from 2005 to 2010 ($p = 0.002$), multivariate analysis revealed widespread variation between the treating hospitals ($p = 0.001$), and even between high-volume hepatopancreatobiliary hospitals ($p = 0.0006$). Younger age, positive lymph nodes, and positive surgical resection margins predicted an increased likelihood of receiving adjuvant treatment. Among patients receiving adjuvant treatment, positive margins and a low comorbidity burden were associated with CRT compared with CTX.

Conclusions Interinstitutional medical practice variation contributes significantly to differential patterns in the rate of adjuvant treatment for PCC. Whether such variation is warranted or unwarranted requires further investigation.

Key Words Pancreatic cancer, adjuvant chemotherapy, combined-modality therapy, medical practice variation, population analyses

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INTRODUCTION

Pancreatic adenocarcinoma (PCC) remains a challenging disease to treat, with almost all patients being diagnosed at an advanced stage[1]. A few patients achieve long-term cure of their disease through surgical resection of their tumour[2]. Based on the results of several randomized controlled trials[3–6], adjuvant systemic therapy—chemotherapy (CTX) or chemoradiation therapy (CRT)—is recommended after surgery to improve survival. Nevertheless, reports of patients undergoing resection for PCC reveal that up to 50% receive no adjuvant treatment, but just observation (OBS) after curative-intent surgery[7–9].

Previous investigations have identified greater age, major perioperative complications, poor preoperative performance status, and favourable histopathologic features as predictors of not receiving adjuvant treatment[7,10–12]; however, the literature is limited to studies performed at

Correspondence to: Natalie Groce Coburn, 2075 Bayview Avenue, Room T2-11, Toronto, Ontario M4N 3M5.
E-mail: natalie.coburn@sunnybrook.ca **DOI:** http://dx.doi.org/10.3747/co.23.3205

a single institution or a small group of institutions, which might not reflect findings at a population level, where patients are treated by disparate practitioners with varying practice and referral patterns[13]. Although population-level analyses have been reported[7,11,12], those analyses lack the granular histopathologic details that have been shown to influence use of adjuvant treatment[10]. We therefore sought to identify, at the population level, independent predictors of receiving adjuvant CTX or CRT, or OBS in patients undergoing curative-intent resection of PCC. By performing the analysis in a single-payer universal health care system, financial barriers to treatment (namely, insurance status) are theoretically controlled for, permitting a unique analysis of the use of adjuvant treatment for adenocarcinoma.

METHODS

Using the Ontario Cancer Registry, patients undergoing surgical resection for PCC in the province of Ontario (population 13 million) between January 2005 and 2010 were identified using *International Classification of Diseases,* revision 9, location codes for the pancreas, plus *International Classification of Diseases for Oncology* morphology codes. The patients thus identified were linked to prospectively-maintained administrative databases at the Institute for Clinical Evaluative Sciences. Those databases included the Discharge Abstract Database maintained by the Canadian Institute for Health Information (contains in-hospital procedures and diagnoses), the medical claims database maintained by the Ontario Health Insurance Plan [OHIP (contains physician billing claims and diagnoses)], the Registered Persons Database (contains sociodemographic information and death certificates), and the Cancer Activity Level Reporting database maintained by the Ontario Cancer Registry (contains medications administered to cancer patients, including radiation). Through those databases, the universal single-payer health care system in Ontario can capture details for all health care encounters, hospitalizations, procedures, and prescription medications dispensed (including chemotherapy and radiation) for all patients treated for PCC. The same methods have previously been described for other cancers[14,15]. Patients were followed until 31 March 2012. Pathology reports for resection specimens were obtained from the Ontario Cancer Registry, abstracted using a digital abstraction tool based on the 2013 College of American Pathologists protocol[16], and validated by independent abstraction of 15% of the reports.

Using Discharge Abstract Database incodes, with confirmation from resection specimen pathology reports, patients undergoing pancreaticoduodenectomy or distal pancreatectomy were identified for inclusion in the cohort. Patients were excluded if they met any of these criteria: age less than 18 years or greater than 99 years; non-adenocarcinoma histology; diagnosis of any other cancer within the preceding 5 years; death within 6 months of undergoing surgery (unlikely to be candidates for adjuvant treatment); and receipt of neoadjuvant therapy (might obfuscate histopathologic evaluation).

Patients were defined as having received adjuvant CTX or CRT based on physician billing codes (OHIP) for chemotherapy infusion or radiation treatment planning within 120 days of surgery. The OHIP database records all physician claims in Ontario for patients treated for PCC. Adjuvant regimens were defined by examining the intervals between chemotherapy infusion dates. Radiation was defined using the dates of radiation treatment planning. Patients who had at least 2 chemotherapy billing codes separated by at least 1 week were classified as having received CTx; those who also had radiation codes within 12 weeks of adjuvant chemotherapy were classified as having received CRT. Patients receiving both systemic CTX and combined CRT were categorized as CRT. Patients who had no billing codes for chemotherapy in the first 120 days after surgery, and those who received less than 1 week of chemotherapy were designated OBS.

The use of OHIP codes to define receipt of adjuvant therapy has previously been described[14,17]. The OHIP database for physician billing records neither the type of chemotherapy administered nor the dose and radiation fractions delivered, although, based on clinical guidelines in use at the time, the chemotherapy regimens consisted of gemcitabine or 5-fluorouracil with folinic acid. Adjuvant therapy definitions based on OHIP codes were compared with patient medication records (Cancer Activity Level Reporting), which demonstrated more than 90% concordance for the available years (2007–2010). The timing and sequence of all OHIP and Cancer Activity Level Reporting codes were reviewed for each individual patient by one author (DJK) to ensure accurate classification.

Baseline demographic characteristics, including age, sex, comorbidity [measured using the Johns Hopkins Adjusted Clinical Groups system score (used with permission)][18,19], rurality status, and median income quintile were recorded. The location of a patient's primary residence was determined using the postal code and was aggregated into a geographic region corresponding to a governmentally-designated local health integration network (http://www.lhins.on.ca/home.aspx), through which all health services are organized and delivered in Ontario[15,20]. Receipt of treatment at 1 of the 10 designated high-volume hepatopancreatobiliary (HPB) centres was also recorded, with all patients not treated at such a centre being grouped into a single category. Histopathologic and operative characteristics were obtained from pathology reports, including the type of resection, the TNM stage, tumour grade, lymphovascular invasion, perineural invasion, microscopic tumour extension, margin status, number of lymph nodes examined, number of lymph nodes positive for disease, and portal or superior mesenteric vein resection and invasion. Using those data, hybrid variables were generated: socioeconomic status (based on rurality and median income quintile) and nodal status (based on lymph node positivity ratio and number of nodes examined). Postoperative complications were identified using a combination of physician billing data for procedures and diagnoses, cross-referenced with Discharge Abstract Database data, to generate a score from 0 to 4 based on the Clavien–Dindo classification[21]. Patients were assigned a score according to the most severe complication experienced.

Baseline sociodemographic, histopathologic, and perioperative characteristics of the cohort are presented by adjuvant treatment group. Univariate associations between

individual clinicopathologic factors and use of CTX, CRT, or OBS were identified using the chi-square and Fisher exact tests. Binary logistic regression modelling was performed using backward elimination of variables at $p \geq 0.2$, with the outcomes of interest being use of adjuvant therapy (CTX or CRT) compared with OBS, and use of CTX compared with CRT. For the logistic regression analyses, patient age was treated as a continuous variable.

A p value less than 0.05 was considered significant. All tests were 2-tailed and were performed using the SAS software application (version 9.2: SAS Institute, Cary, NC, U.S.A.). Research ethics board approval for the study was obtained from the appropriate institutional review committees.

RESULTS

The database search identified 473 patients undergoing curative-intent resection for PCC in Ontario between January 2005 and 2010. Independent validation of the pathology report abstraction demonstrated a pooled kappa of 0.83. Of the identified patients, 397 survived for more than 6 months after surgery and were designated the analysis cohort. Tables I and II present baseline sociodemographic, clinical, and histopathologic characteristics for this cohort, subdivided by adjuvant treatment. Of the 397 patients analyzed, 299 underwent adjuvant treatment (75.3%), and 98 underwent OBS (24.7%); of those receiving adjuvant treatment, 108 received CRT (36.1%) and 191 received CTX (63.9%). On unadjusted analysis, 84% of patients 60 years of age or less received some form of adjuvant therapy; only 31% of patients 81 years of age and older received adjuvant treatment ($p = 0.0002$). Of patients with negative margins, 19% received CRT; 48% with positive margins received CRT ($p < 0.0001$). Over the course of the study period, the percentage of patients receiving CRT was observed to increase (to 39% from 20%); a concomitant decrease in the percentage of patients not receiving adjuvant therapy occurred (to 13% from 42%, $p = 0.009$).

Figures 1 and 2 depict the geographic distribution, based on region of residence, of patients receiving OBS and CRT respectively. Rates of adjuvant treatment use (CTX or CRT) ranged from 60% to 90%. Rates of CTX ranged from 26% to 75%, and of CRT, from 7% to 44%. In 3 local health integration networks, more patients received CRT than CTX. A clear association between adjuvant treatment use and proximity to a major metropolitan centre was not observed. Similar rates of adjuvant treatment were observed for some patients residing in lower-density Northern Ontario as for some residing in higher-density Southern Ontario (60%–70%); other Northern Ontario regions demonstrated adjuvant treatment rates between 80% and 90%. A relationship between use of adjuvant treatment and proximity to a designated HPB centre (which cluster in large urban areas) was similarly not observed.

Table III presents independent predictors of adjuvant treatment use (either CTX or CRT) compared with OBS use (factors that remain predictive of adjuvant treatment once other relevant factors have been adjusted for). Positive surgical resection margins were associated with an increased likelihood of adjuvant treatment use [odds ratio (OR): 2.191;

TABLE I Baseline patient characteristics of the included cohort surviving 6 months or more after curative-intent resection of pancreatic adenocarcinoma

Variable	Patient group [*n* (%)]		
	CRT	CTx	OBS
Patients	108	191	98
Age[a]			
≤60 Years	47 (33)	72 (51)	23 (16)
61–70 Years	39 (28)	68 (49)	31 (22)
71–80 Years	21 (20)	48 (46)	35 (34)
≥81 Years	<6	<6	9 (69)
Sex			
Women	52 (26)	99 (50)	46 (23)
Men	56 (28)	92 (46)	52 (26)
Comorbidity (ACG score)[a]			
0–9	61 (37)	68 (42)	34 (21)
10–32	47 (20)	123 (53)	64 (27)
Socioeconomic status			
Rural	21 (37)	18 (32)	18 (32)
Urban quintile 1	11 (22)	23 (46)	16 (32)
Urban quintile 2	25 (33)	33 (44)	17 (23)
Urban quintile 3	13 (20)	41 (62)	12 (18)
Urban quintile 4	19 (25)	36 (48)	20 (27)
Urban quintile 5	19 (26)	40 (54)	15 (20)
Surgical resection			
Pancreaticoduodenectomy	99 (28)	167 (48)	82 (24)
Distal pancreatectomy	9 (18)	24 (49)	16 (33)
Perioperative complication (Clavien–Dindo classification)			
0–1	63 (27)	126 (53)	47 (20)
2	9 (35)	10 (38)	7 (27)
3A	9 (22)	17 (42)	15 (37)
3B	15 (33)	17 (37)	14 (30)
4	12 (25)	21 (44)	15 (31)
Surgery at HPB centre[b]			
HPBC01	10 (10)	69 (66)	26 (25)
HPBC02	17 (27)	25 (40)	21 (33)
HPBC03	18 (38)	18 (38)	11 (23)
HPBC04	20 (48)	18 (43)	<6
HPBC05	<6	25 (76)	<6
HPBC06	<6	<6	7 (58)
HPBC07	<6	10 (62)	<6
HPBC08	<6	7 (64)	<6
HPBC09	<6	<6	<6
HPBC10	<6	<6	6 (55)
Non-HPB centre	24 (51)	12 (26)	11 (23)
Year of surgery[a]			
2005	14 (20)	27 (38)	30 (42)
2006	13 (19)	37 (54)	18 (26)
2007	24 (28)	42 (49)	20 (23)
2008	24 (28)	43 (50)	19 (22)
2009	30 (39)	37 (48)	10 (13)
2010	<6	<6	<6

[a] $p < 0.01$.

[b] Unable to compare all 3 levels of treatment by chi-square or Fisher exact test.

CRT = chemoradiation therapy; CTx = chemotherapy; OBS = observation; ACG = adjusted clinical group; HPB = hepatopancreatobiliary.

95% confidence interval (CI): 1.104 to 4.345], and increasing age was associated with a decreased likelihood of adjuvant treatment (OR: 0.924; 95% CI: 0.895 to 0.953). Lymph nodes positive for malignant disease were also predictive of adjuvant treatment use ($p = 0.005$). Compared with 2005, later years showed that the likelihood of adjuvant treatment use increased by factors in the range of 2–7 ($p = 0.002$). Variation in the likelihood of adjuvant treatment use was widespread between treating institutions (HPB centres and non-centres alike, $p = 0.001$); point estimates of the ORs ranged from 0.055 to 2.950. Patient and treatment characteristics not significantly associated with use of adjuvant therapy included comorbidity burden, socioeconomic status, and sex.

TABLE II Baseline tumour characteristics of the included cohort surviving 6 months or more after curative-intent resection of pancreatic adenocarcinoma

Variable	Patient group [*n* (%)]		
	CRT (*n*=108)	CTx (*n*=191)	OBS (*n*=98)
T Stage			
T1	<6	10 (50)	<6
T2	22 (29)	27 (36)	27 (36)
T3	78 (27)	152 (52)	63 (22)
T4	<6	<6	<6
Tx	<6	<6	<6
Nodal status[a]			
N0	24 (21)	44 (39)	44 (39)
N1, LNPR<0.2	40 (30)	67 (50)	27 (20)
N1, LNPR≥0.2	39 (30)	71 (54)	22 (17)
N1x, incalculable LNPR	<6	9 (47)	<6
M Stage			
M0/Mx	106 (28)	184 (48)	96 (25)
M1	<6	7 (64)	<6
Microscopic invasion			
Absent	25 (29)	33 (38)	28 (33)
Present	80 (27)	146 (50)	66 (23)
Indeterminate or unknown	<6	12 (63)	<6
Lymphovascular invasion			
Absent	34 (27)	60 (48)	32 (25)
Present	57 (31)	84 (46)	42 (23)
Indeterminate or unknown	17 (19)	47 (53)	24 (27)
Perineural invasion[b]			
Absent	<6	13 (50)	9 (35)
Present	96 (31)	148 (47)	70 (22)
Indeterminate or unknown	8 (14)	30 (53)	19 (33)
Tumour grade			
Well differentiated	24 (33)	31 (42)	18 (25)
Moderately differentiated	60 (24)	131 (52)	60 (24)
Poorly differentiated	23 (33)	28 (41)	18 (26)
Indeterminate or unknown	<6	<6	<6
Resection margin status[c]			
Negative	52 (19)	148 (53)	79 (28)
Positive	56 (48)	43 (36)	19 (16)
Vein resection and invasion			
No resection	87 (26)	164 (49)	83 (25)
Resection without invasion	11 (31)	16 (46)	8 (23)
Resection with invasion	10 (36)	11 (39)	7 (25)

[a] $p < 0.01$.
[b] $p < 0.05$.
[c] $p < 0.0001$.
CRT = chemoradiation therapy; CTx = chemotherapy; OBS = observation; LNPR = lymph node positivity ratio.

Table IV presents independent predictors of CTX use compared with CRT use for the 299 patients receiving adjuvant treatment (1 patient is excluded because of an uncategorizable T stage). An adjusted clinical groups comorbidity score of 10 or higher was associated with an increased likelihood of CTX use (OR for CTX vs. CRT: 2.498; 95% CI: 1.362 to 4.581). A positive resection margin identified on final pathology was associated with a decreased likelihood of receiving CTX (OR: 0.226; 95% CI: 0.117 to 0.436), as was rural location of primary residence compared with residence in the highest-income urban locations (OR: 0.322; 95% CI: 0.113 to 0.915). Tumour grade and nodal status were not associated with adjuvant treatment regimen.

DISCUSSION

In the present study, we used linked administrative databases and resection specimen pathology reports for a large population supported by a single-payer universal health care system to identify sociodemographic, clinicopathologic, and perioperative factors associated with use of adjuvant treatment compared with OBS, and of adjuvant CTX compared with adjuvant CRT. Between 2005 and 2010, the proportion of patients receiving adjuvant treatment after resection increased, an observation that persisted on multivariate analysis. Adoption of adjuvant treatment might relate to the publication of randomized trials demonstrating improved overall and disease-free survival with administration of adjuvant therapy[3,5,6,22]. Compared with previous population-level analyses conducted using data from the United States, the analyses in the present study showed that a substantially greater proportion of patients received adjuvant treatment (75% vs. 55%–58%), although the proportion reported here was similar to that in a more recent population-based study conducted in Australia (76%)[8,9,23]. Possible explanations for the foregoing observations include the temporal trend of increasing rates of adjuvant treatment observed in the current study, as well as the availability of public health insurance covering the costs of adjuvant treatment in Canada and Australia.

Substantial heterogeneity between institutions (including between designated HPB centres) was demonstrated for the likelihood of receiving adjuvant treatment and the likelihood of receiving CTX compared with CRT, even after exclusion of early postoperative deaths and adjustments for other pertinent factors. During the study period, increasing numbers of pancreatic operations were performed at designated HPB centres, with the goal of ameliorating postoperative outcomes; and yet, variation in the likelihood of receiving adjuvant treatment

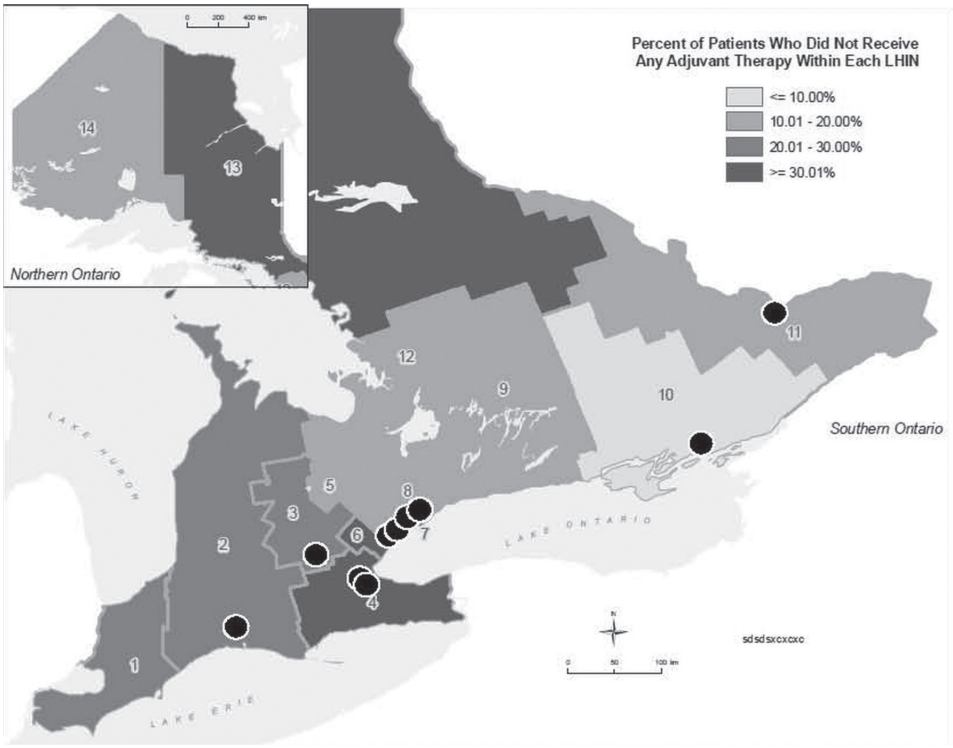

FIGURE 1 Distribution of patients not receiving adjuvant therapy, by geographic region of primary residence. Black circles denote designated hepatopancreatobiliary centres. LHIN = local health integration network.

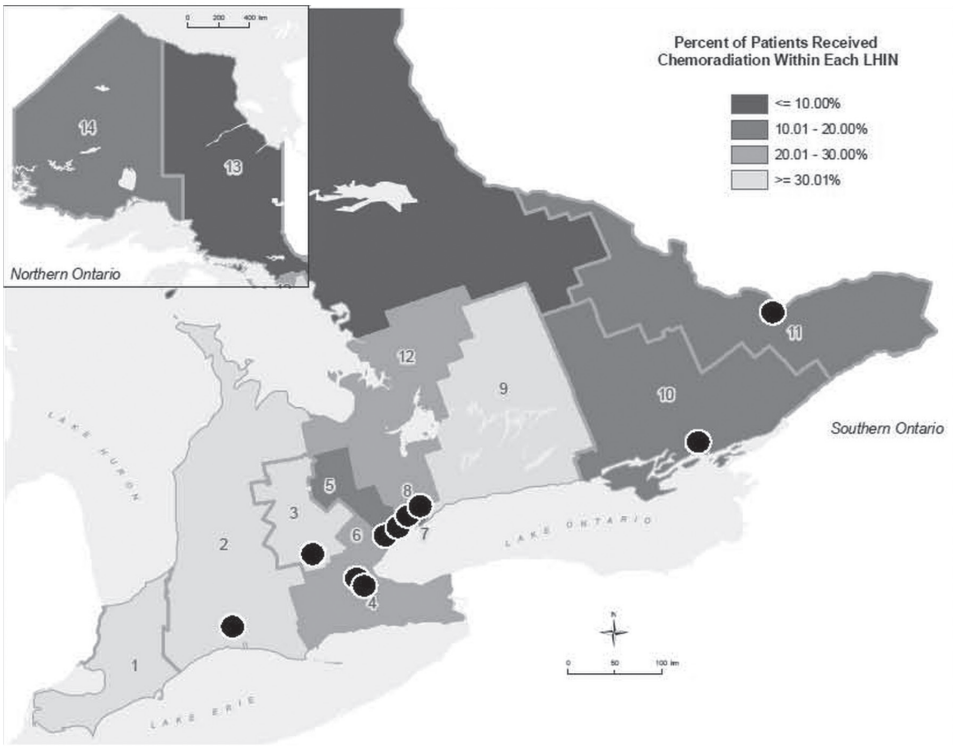

FIGURE 2 Distribution of patients receiving adjuvant chemoradiation therapy, by geographic region of primary residence. Black circles denote designated hepatopancreatobiliary centres. LHIN = local health integration network.

persisted, even after adjustment for year of surgery. Those findings imply medical practice variation attributable to institution-specific practice patterns, both in terms of patients receiving adjuvant treatment compared with OBS, and in terms of patients receiving CTX compared with CRT. Indeed, a recent analysis of PCC treatment at a

TABLE III Independent predictors of receipt of adjuvant treatment (chemotherapy or chemoradiation therapy) compared with observation after resection of pancreatic adenocarcinoma[a]

Variable	OR	95% CI	
		Lower	Upper
Age[b]	0.92	0.90	0.95
Year of surgery[c]			
2005	Reference		
2006	1.86	0.80	4.33
2007	2.79	1.24	6.28
2008	2.77	1.24	6.21
2009	6.95	2.63	18.36
2010	16.68	1.53	182.10
Nodal status[c]			
N0	Reference		
N1, LNPR<0.2	2.59	1.30	5.16
N1, LNPR≥0.2	3.25	1.60	6.64
N1x, incalculable LNPR	3.02	0.80	11.48
Resection margin status[d]			
Negative	Reference		
Positive	2.19	1.10	4.34
Perioperative complication (Clavien–Dindo classification)			
0–1	Reference		
2	0.64	0.20	2.10
3A	0.46	0.19	1.12
3B	0.35	0.14	0.86
4	0.48	0.20	1.18
Surgery at HPB centre[c]			
Non-HPB centre	Reference		
HPBC01	0.66	0.24	1.84
HPBC02	0.37	0.13	1.07
HPBC03	0.71	0.22	2.28
HPBC04	2.92	0.74	11.53
HPBC05	2.95	0.61	14.30
HPBC06	**0.06**	**0.01**	**0.28**
HPBC07	0.69	0.13	3.50
HPBC08	1.05	0.15	7.42
HPBC09	0.67	0.10	4.62
HPBC10	**0.20**	**0.04**	**0.96**

[a] Results of multivariate logistic regression with backward elimination of covariates at $p > 0.2$ (comorbidity, M stage, tumour grade, vein resection and invasion, microscopic invasion, sex, surgical resection, socioeconomic status, T stage, perineural invasion, lymphovascular invasion); 397 patients; C statistic: 0.818; chi-square residual: $p = 0.67$. Boldface type indicates significance.
[b] $p < 0.0001$.
[c] $p < 0.01$.
[d] $p < 0.05$.
OR = odds ratio; CI = confidence interval; LNPR = lymph node positivity ratio; HPB = hepatopancreatobiliary.

TABLE IV Independent predictors of receipt of chemotherapy compared with chemoradiation therapy after resection of pancreatic adenocarcinoma[a]

Variable	OR	95% CI	
		Lower	Upper
Age	1.02	0.99	1.06
Year of surgery			
2005	Reference		
2006	2.34	0.75	7.30
2007	0.65	0.23	1.82
2008	0.69	0.25	1.92
2009	0.58	0.21	1.57
2010	0.75	0.11	4.91
Comorbidity (ACG score)[b]			
0–9	Reference		
10–32	2.50	1.36	4.58
Socioeconomic status[b]			
Urban 5	Reference		
Rural	0.32	0.11	0.92
Urban 1	2.33	0.77	7.07
Urban 2	0.78	0.30	2.00
Urban 3	2.67	0.92	7.77
Urban 4	1.21	0.46	3.14
Resection margin status[c]			
Negative	Reference		
Positive	0.23	0.12	0.44
Surgery at HPB centre[c]			
Non-HPB centre	Reference		
HPBC01	11.88	4.12	34.25
HPBC02	4.20	1.46	12.01
HPBC03	2.50	0.84	7.42
HPBC04	1.20	0.42	3.43
HPBC05	12.24	2.98	50.34
HPBC06	1.81	0.21	15.64
HPBC07	10.06	1.70	59.74
HPBC08	18.52	2.40	142.60
HPBC09	1.18	0.15	9.01
HPBC10	1.44	0.16	12.62

[a] Results of multivariate logistic regression with backward elimination of covariates at $p > 0.2$ (perineural invasion, lymphovascular invasion, sex, vein resection and invasion, T stage, microscopic invasion, postoperative complication, nodal status, tumour grade, M stage, surgical resection); 298 patients; C statistic: 0.837; chi-square residual: $p = 0.90$. Boldface type indicates significance.
[b] $p < 0.01$.
[c] $p < 0.0001$.
OR = odds ratio; CI = confidence interval; ACG = adjusted clinical group; HPB = hepatopancreatobiliary.

single Ontario institution noted the prevailing historical practice of not referring patients for adjuvant radiation, possibly relating to the publication of evidence supporting the role of CTX alone during the study period[5,22,24,25]. Such referral patterns and institutional biases might partly underlie the observed geographic variation in rates and types of adjuvant treatment administered. The HPB centres are primarily responsible for the perioperative care of patients, with adjuvant treatment often delivered at other hospitals closer to a patient's primary residence; however, communication facilitated by multidisciplinary conferences between the HPB centres and the hospitals delivering adjuvant treatment might result in practice patterns at the HPB centres influencing care at non-centre hospitals.

Although some practice variation is warranted and reflects a health care system responsive to the needs and preferences of patients, unwarranted variation points to potential equity and efficiency issues within a health care system[26,27]. As has been hypothesized by Wennberg and Gittelsohn, physician uncertainty about treatment effectiveness often underlies variation in utilization patterns[28]. Many randomized trials have demonstrated an association of improved overall survival with adjuvant treatment, but others have been unable to[3–6,22,29]. Moreover, the absolute survival benefit conferred by adjuvant treatment is debated, having been reported to be as low as 4–5 months in some series[29–31]. In the context of the dismal prognosis faced by PCC patients, conflicting reports of the effectiveness of adjuvant therapy might contribute to reluctance on the part of providers to utilize it. Other potential causes of unwarranted practice variation include a differential availability of resources, termed "supply-sensitive variation," which suggests inequity in the health care system[26]. By controlling for the influence of health insurance status, the present study has identified other putative causes of differential use of adjuvant treatment and differential use of CTX compared with CRT, and has highlighted a possible inequity in spite of a single-payer universal health care program. Further investigation into the cause of the observed institutional practice variation—and whether it is appropriate—is needed.

A progressively worse lymph node positivity ratio was also associated with increased likelihood of receiving adjuvant treatment[32]. Those findings might relate to the hypothesis that patients with nodal disease derive the greatest benefit from adjuvant treatment[9,33,34]. Conversely, others have argued that patients with node-negative disease benefit most from adjuvant treatment, underscoring a controversy in patient selection[22]. Interestingly, tumour grade was not associated with use of adjuvant treatment in spite of evidence identifying grade as a putative determinant of response to adjuvant treatment[9,34].

The interplay between resection margin status, adjuvant treatment, and overall survival remains controversial. Prior analyses have suggested that positive resection margins are associated with an increased likelihood of adjuvant treatment use[8,10]. A meta-analysis of randomized controlled trials reported that R0 patients benefited from adjuvant CTX compared with adjuvant CRT, and that R1 patients derived greatest benefit from CRT[35]. The results of the present study suggest a strong tendency to administer adjuvant treatment, particularly CRT, to patients with positive margins[35].

To our knowledge, the present work is the first population-based study to identify predictors of the use of adjuvant treatment for PCC with incorporation of granular pathology report details and the ability to determine all treatments received by all patients in the cohort. Strengths of the study include the large cohort size and inclusion of patients treated at disparate institutions with varying practice patterns across a large geographic region within a single-payer health care system. The population-level analyses previously reported[7,11,12] lack the histopathologic details provided by the pathology reports used here. The results are therefore more reflective of the actual care received and the outcomes experienced than are the results of studies conducted at a single institution or selected groups of institutions; they are consequently also more generalizable. Limitations include the heterogeneity of the treatment regimens; the lack of information about the specific chemotherapeutics delivered; the rationale for treatment delivery, delay, or discontinuation; and the potential selection bias and confounding-by-indication inherent to this type of retrospective study. Information about patient performance status—a factor that undoubtedly influences use of adjuvant treatment—was also unavailable for our study. Furthermore, some patients in the cohort might have been included in clinical trials that were ongoing during the study period, although the number of patients potentially enrolled is estimated to be less than 5%. Additionally, the small number of patients treated at the smaller HPB institutions suggests that conclusions about those hospitals should be interpreted with caution and that the variation demonstrated should be the primary focus of the analysis.

CONCLUSIONS

In the present study, we analyzed predictors of adjuvant treatment use after resection for PCC, identifying substantial variation between hospitals and between geographic regions in the likelihood of receiving adjuvant treatment. Given the increasing emphasis on standardization of medical care to improve quality and outcomes, as well as to minimize the financial and personal costs of less-effective medical care, further investigation into medical practice variation and its causes is needed in this area.

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The cohort on which this analysis is based was the subject of another publication by NGC and her research team [Kagedan DJ, Raju RS, Dixon ME, *et al.* The association of adjuvant therapy with survival at the population level following pancreatic adenocarcinoma resection. *HPB (Oxford)* 2016;18:339–47]. However, the study objectives, analyses performed, results presented, and conclusions drawn are unique and distinct.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Division of General Surgery, Department of Surgery, University of Toronto, Toronto, ON; †Department of Surgery, Maimonides Medical Center, Brooklyn, NY, U.S.A.; ‡Sunnybrook Health Sciences Centre, §Institute for Clinical Evaluative Sciences, and ‖Faculty of Medicine, University of Toronto, Toronto, ON; #Department of Surgery, Saint Barnabas Medical Center, Livingston, NJ, U.S.A.; **Institute of Health Policy, Management and Evaluation, University of Toronto, and ††Health Outcomes and PharmacoEconomic (HOPE) Research Centre, Sunnybrook Research Institute, Toronto, ON.

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