



Impact of surveillance among patients with resected pancreatic cancer following adjuvant chemotherapy

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Background: Pancreatic adenocarcinoma carries a high risk of recurrence even after surgery and adjuvant chemotherapy. Current guidelines do not endorse routine surveillance imaging due to lack of evidence supporting a survival benefit. With current first-line palliative chemotherapy options, it is unclear whether surveillance allows for early detection of asymptomatic disease and therefore an improved opportunity to offer chemotherapy to fit patients. We sought to describe patterns of surveillance of resected pancreatic cancer at British Columbia (BC) Cancer and determine whether utilization of computerized tomography (CT) scans affected likelihood of receiving palliative chemotherapy at the time of recurrence.

Methods: A retrospective review was completed to identify patients treated at BC Cancer centres between 2010–2016 who had undergone curative intent resection and received at least one cycle of adjuvant chemotherapy. Information was collected on baseline characteristics, imaging scans done between adjuvant chemotherapy and recurrence, and receipt of palliative chemotherapy. Two cohorts were defined based on number of scans done between completion of adjuvant chemotherapy and recurrence: those with only 1 scan were defined as “symptomatic” recurrences and patients who had undergone more than 1 scan were considered “surveillance” recurrences.

Results: In total, 142 patients were included of which 115 (81%) patients developed recurrence. There were 22 patients (19%) in the “symptomatic” cohort and 93 patients (81%) in the “surveillance” cohort. Median time to recurrence 274 days (9.1 months) in the symptomatic cohort compared to 471 days (15.7 months) in the surveillance group. Patients who underwent surveillance scans were more likely to receive palliative chemotherapy at the time of recurrence, though statistical significance was not reached: 51% in surveillance group versus 27% in symptomatic group [odds ratio (OR) 2.11, 95% confidence interval (CI): 0.75–6.58, P=0.17].

Conclusions: Despite the absence of surveillance recommendations, the majority of patients underwent surveillance imaging. We demonstrated a non-significant increase in the likelihood of receiving palliative chemotherapy among patients who underwent surveillance scans. With more efficacious palliative chemotherapy options available, studies to determine whether receipt of chemotherapy in asymptomatic recurrences translates into improved survival and/or quality of life are warranted.

Keywords: Surveillance; pancreatic cancer; adjuvant

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy that is associated with significant morbidity and mortality (1,2). Although the majority of patients have unresectable or metastatic disease at the time of presentation, a minority of patients present with localized, resectable disease (3). In these cases, surgical resection, often followed by adjuvant chemotherapy, remains the only potentially curative treatment option. Despite improvements in treatments, 5-year survival rates remain low at less than 10% (4). Patients are at high risk of recurrence even after surgical resection and adjuvant chemotherapy.

In other solid tumors such as colorectal cancer, postoperative surveillance is associated with earlier detection of recurrence and increased likelihood of receiving potentially curative surgery at the time of recurrent or metastatic disease, which is the basis for the recommendation of scheduled colorectal cancer surveillance in national guidelines (5-8). In contrast, guidelines for surveillance in resected pancreatic cancer are heterogeneous and the role of serial surveillance imaging remains undefined. Lack of consensus has led to significant variations in surveillance practices among providers (9-11). Even among national guidelines, discrepancies exist as recommendations are derived from expert opinion and lack high-level evidence (12). While the National Comprehensive Cancer Network (NCCN) recommends surveillance every 3–6 months for 2 years (history/physical, CA19-9, and imaging), then every 6–12 months as clinically indicated (13), the American Society of Clinical Oncology (ASCO) suggests regular visits at 3- or 6-month intervals in order to monitor for recovery of treatment-related toxicities and recurrence. The role of imaging, prolongation of surveillance intervals, and duration of surveillance are undefined (14). As for the European Society of Medical Oncology (ESMO) guidelines, they recommend no role for regular follow up after initial therapy (15).

With recent advances in available first-line palliative chemotherapy options for recurrent pancreatic cancer (16,17) and recognizing that patient performance status is a key determinant of ability to receive combination chemotherapy, it is unknown whether performing surveillance imaging might allow for earlier detection of asymptomatic disease, and therefore an opportunity for patients to receive more efficacious palliative chemotherapy. In this study, we describe the patterns of surveillance in patients followed at a Canadian provincial cancer agency to

determine whether imaging after adjuvant chemotherapy is associated with receipt of palliative chemotherapy upon disease recurrence. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jgo-20-422>).

Methods

Population

British Columbia (BC) Cancer is the provincial cancer agency for the province of BC, Canada with distributed sites across the province. Following research ethics board approval, a retrospective review was completed to identify patients treated at BC Cancer centres between January 1, 2010 and December 31, 2016 who had undergone curative intent resection and received at least one cycle of adjuvant chemotherapy. Both pancreatic and periampullary cancers were included, although we hereinafter refer to the studied sample population as “pancreatic cancers”. Patients were excluded if they recurred during or within 28 days after completing adjuvant chemotherapy and/or had multiple simultaneous cancer diagnoses.

Data collection

Baseline characteristics, number of imaging scans done between completing adjuvant chemotherapy and date of recurrence, and receipt of palliative chemotherapy were collected by manual chart review. Disease recurrence and date of recurrence were determined radiographically (i.e., date of first imaging study demonstrating disease recurrence/metastatic disease).

Statistical analysis

The primary endpoint of the study was estimation of the probability of receipt of palliative chemotherapy using multivariable logistic regression while adjusting for other factors such as age, sex, and the type of scan (surveillance *vs.* symptomatic). Two cohorts were defined based on number of scans done between completion of adjuvant chemotherapy and recurrence: those with only 1 scan were defined as “symptomatic” recurrences and patients who had undergone more than 1 scan were considered “surveillance” recurrences. These cohorts were established to differentiate patients who likely underwent a scan as guided by high clinical suspicion of recurrence (i.e.,

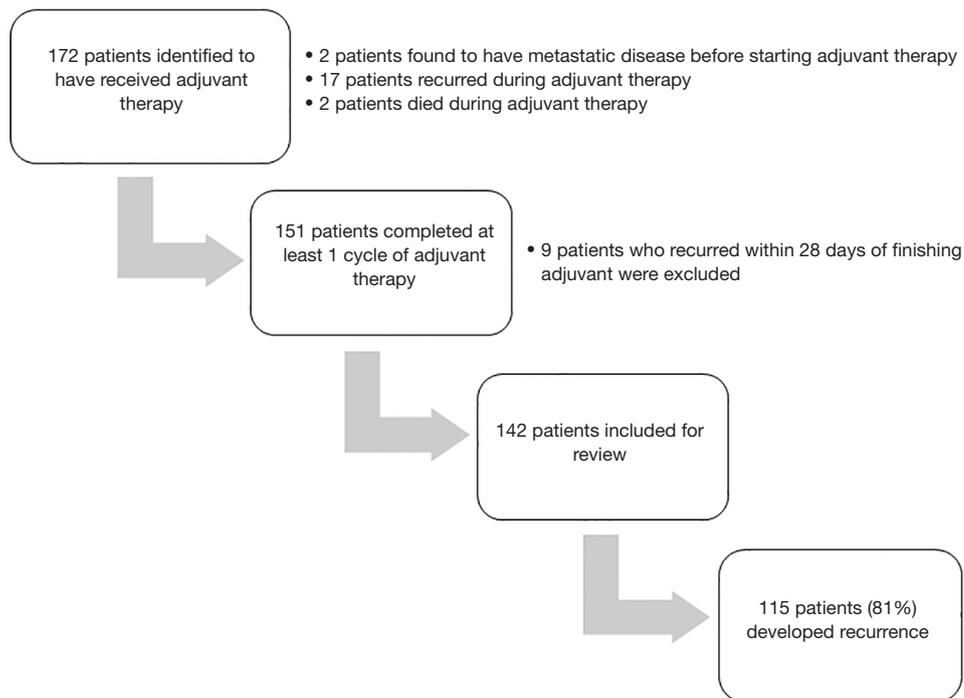


Figure 1 Flowchart of patients included in study.

presence of symptoms) versus those who underwent serial scans for reasons unrelated to new onset symptoms (i.e., surveillance). Difference in survival of the cohorts was not assessed as the variable of interest (number of scans) was confounded with survival: a patient with longer survival is likely to have more scans over the longer follow-up and a patient with aggressive disease is likely to have a higher number of scans in a short timeframe. Patient, tumour, and treatment characteristics between the cohorts were compared using the chi-square test for categorical variables and the median test for continuous variables. Statistical significance was defined as a two-sided P value <0.05. SAS 9.4 (SAS Institute, Cary, NC, USA) and R 3.5.1 was used for all statistical analysis.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by University of BC Cancer Agency Research Ethics Board, H18-03243, and individual consent for this retrospective analysis was waived.

Results

A total of 142 eligible patients followed at BC Cancer were identified, of which 115 (81%) patients had recurrence (*Figure 1*).

Among those with only 1 scan, defined as “symptomatic” recurrences: 22 patients (19%), median age 68 years, 64% female, and 91% node-positive. Within this cohort, median time to recurrence was 274 days (9.1 months) and 95% of them occurred within the first 2 years. As for patients with “surveillance” recurrences: 93 patients (81%), median age 64 years, 43% female, 81% node-positive, median number of scans 3. Median time to recurrence was 471 days (15.7 months) and 74% occurred within the first 2 years (*Table 1*).

Patients who underwent surveillance scans were more likely to receive palliative chemotherapy at the time of recurrence, but statistical significance was not reached: 51% in surveillance group versus 27% in symptomatic group [odds ratio (OR) 2.11, 95% confidence interval (CI): 0.75–6.58, P=0.17]. Younger patients and males were more likely to receive palliative chemotherapy, although not statistically

Table 1 Baseline patient characteristics in 115 (81%) patients who developed recurrence: symptomatic versus surveillance cohorts. P values between the two cohorts for each of the baseline characteristics were done, none of which met the 0.05 level of statistical significance

Baseline characteristics	Symptomatic, (n=22, 19%)	Surveillance, (n=93, 81%)
Median age, years	68	64
Sex, n [%]		
Female	14 [64]	40 [43]
Male	8 [36]	53 [57]
Tumor stage, n [%]		
T1	2 [9]	4 [4]
T2	6 [27]	10 [11]
T3	14 [64]	71 [76]
T4	0 [0]	8 [9]
Nodal status, n [%]		
N0	2 [9]	16 [17]
N1	20 [91]	75 [81]
Unknown	0 [0]	2 [2]
Tumor grade, n [%]		
1	2 [9]	5 [5]
2	6 [27]	61 [66]
3	14 [64]	26 [28]
Unknown	0 [0]	1 [1]
Resection margins, n [%]		
R0	14 [64]	65 [70]
R1	7 [32]	27 [29]
R2	1 [5]	1 [1]
Site of primary tumour, n [%]		
Head/neck	16 [73]	63 [68]
Body	5 [23]	21 [23]
Periampullary	1 [5]	9 [10]
Postoperative baseline CA19-9, n [%]		
≤37 units/mL	12 [55]	59 [63]
>37 units/mL	7 [32]	24 [26]
Unknown	3 [14]	10 [11]
Time from surgery to recurrence, n [%]		
<1 year	20 [91]	26 [28]
1–2 years	1 [5]	43 [46]
>2 years	1 [5]	24 [26]

Table 2 Likelihood of receiving palliative chemotherapy

Variable	OR (95% CI)	P value
Older vs. younger age	0.96 (0.92–1.00)	0.04
Male vs. female	2.08 (0.96–4.59)	0.07
Surveillance vs. symptomatic recurrences	2.11 (0.75–6.58)	0.17

significant (*Table 2*).

Discussion

The rationale for surveillance is to detect recurrences early, wherein there remains a window of opportunity to offer cancer-directed interventions and improve patient outcomes. Systemic therapy, which is a cornerstone of treatment in pancreatic cancer, is a continually evolving landscape. In the curative intent setting, what was once primarily a surgical disease now warrants multi-disciplinary review and consideration of neoadjuvant and adjuvant therapies (18–20). In the palliative setting, newer treatment options have led to improvements in median overall survival (16,17,21,22) and patient-reported quality of life (23,24). At BC Cancer, guidelines do not recommend regular surveillance as this has not been shown to confer a survival benefit (25). In our study, the rate of recurrence among patients with resected pancreatic cancer who received at least one cycle of adjuvant chemotherapy was high at 81%. Despite the absence of recommendations, the majority of patients treated with adjuvant chemotherapy for resected pancreatic cancer at BC Cancer did undergo some degree of surveillance imaging. We observed an association between imaging and a higher likelihood of receiving palliative chemotherapy (50% vs. 27%). While it can be surmised that the ability to receive chemotherapy would be associated with an improvement in patient outcomes, larger studies would be required to confirm this and determine whether earlier receipt of chemotherapy in surveillance-detected recurrences results in improvements in survival and quality of life.

Similar to our study investigating likelihood of receiving palliative chemotherapy, Daamen *et al.* undertook a recent Netherlands-based observational cohort study of 836 resected PDAC patients, investigating whether early detection of asymptomatic PDAC recurrence increased likelihood of receiving additional treatment and if receipt of additional treatments translated into improved survival

rates (26). Out of 670 (80%) patients who developed recurrence, 76% were symptomatic and 24% were asymptomatic. Thirty-one percent of symptomatic recurrences received additional treatment (chemotherapy, radiation, or other therapies) compared to 48% of their asymptomatic counterparts. Additional treatment of PDAC recurrence was independently associated with improved OS for both symptomatic and asymptomatic patients: hazard ratio (HR) 0.53, 95% CI: 0.42–0.67, $P < 0.001$ and HR 0.45, 95% CI: 0.29–0.70, $P < 0.001$, respectively.

Numerous other studies have been done to elucidate the relationship between surveillance and survival benefit. These have yielded mixed results and should be interpreted cautiously as there have been ongoing improvements in palliative chemotherapy regimens. A retrospective review of patients with resected ductal adenocarcinoma between 2000 and 2013 was done by Wu *et al.*, investigating differences in median overall survival between four different surveillance strategy groups: symptom group, imaging group, tumor marker group, and intense group (history/physical, tumor markers, and imaging). They did not find any statistical difference between the four subgroups, albeit the authors also acknowledged that more recent advances in palliative chemotherapy, such as FOLFIRINOX, and advances in treatments for local recurrences may not have been encompassed by their patient sample (27). Similarly, Witkowski *et al.* quantified nationwide use of imaging after pancreatic cancer resection and found a doubling in the median number of scans done between 1991 and 2005, but no associated survival benefit (28).

Others have found that surveillance may lead to higher rates of detecting recurrences and improved overall survival. A retrospective review presented as an abstract in 2010 by Shabahang *et al.* compared three groups of patients who underwent different surveillance regimens. Recommended follow-up was defined as serial carbohydrate antigen 19-9 (CA19-9) and computerized tomography (CT) imaging every 3 months in the first year, every 6 months in the second year, and annually thereafter. One group underwent the follow-up as recommended [$n=19$ (14%)], one group had follow-up but not as recommended [$n=82$ (59%)], and finally the last group had elected not to undergo routine follow-up [$n=38$ (27%)]. The median survival periods for the 3 groups were 16.6, 15.7, and 8.7 months, respectively. The authors' conclusions were in support of a scheduled surveillance program (29).

Although we did not collect information regarding the absence or presence of symptoms at the time of recurrence

in our study, one hypothesis why patients who undergo scans may be more likely to receive subsequent palliative chemotherapy is the detection of recurrences while patients are still asymptomatic and clinically fit. Often what precludes physicians from offering chemotherapy to patients, apart from pre-existing medical comorbidities, is their performance status. In a study by Nordby *et al.*, 28% of asymptomatic recurrences received best supportive care only compared to 63% of symptomatic patients (30). Not only are asymptomatic patients more likely to receive oncologic treatments at the time of recurrence compared to their symptomatic counterparts, but early detection could make the difference between a patient being able to tolerate a triplet chemotherapy regimen such as FOLFIRINOX as opposed to single agent regimens. Tzeng *et al.* also described significantly longer median overall survival in asymptomatic recurrences (29.6 *vs.* 18.0 months). Asymptomatic patients were more likely to receive treatment (91.2% *vs.* 61.4%) at the time of recurrence which translated to a significantly longer post-resection overall survival (11.8 *vs.* 2.6 months, $P < 0.001$) (31).

Apart from the opportunity to offer systemic treatments, there may still be a role for early detection of recurrence. At the time of recurrence, preserved performance status and isolated recurrence (local or distant as opposed to regional or multiple-site recurrence) are independently associated with longer post-resection overall survival (31). Symptomatic recurrence, on the other hand, is an independent predictor of poor post-recurrence survival (30). Early detection of limited, locoregional recurrence may also offer the opportunity for surgical interventions. Up to one third of pancreatic cancer recurrences are isolated local recurrences (32–35), and surgical resection could confer survival benefit (36). A study by Tjaden *et al.* demonstrates how structured detection of recurrences facilitates the ability to offer subsequent treatments. In their cohort, they implemented structured, postoperative follow-up after surgery for PDAC: CT scans 3-monthly for 2 years, followed by 6-monthly afterwards. They found that not only was the presence of symptoms an unreliable indicator of recurrence (only 26% of patients had reported symptoms at the time of recurrence), but also that all 74 out of 184 (40%) PDAC patients who recurred went on to receive cancer-directed treatment including 11 of 16 patients who underwent re-resection for local recurrence (37).

Ultimately, consensus regarding the role of surveillance and development of a structured surveillance strategy is

important in the setting of resected pancreatic cancer. Studies investigating surveillance that were done prior to the development of newer palliative chemotherapy regimens may not reflect the full extent of benefits to detecting early, asymptomatic recurrences and the ability to offer subsequent efficacious therapies or opportunity to participate in clinical trials. The development of a surveillance schedule requires multiple considerations including cost-effectiveness (38), modality of surveillance, frequency, and duration. CA19-9 has been previously demonstrated to be predictive of survival (27,39-41), and the observation of its rise preceding detection of recurrence by imaging (42) may be helpful as a more cost-effective surveillance modality than imaging alone. Similar to previous studies which have found the highest risk of recurrence 2 years after surgery (43,44), 78% of recurrences occurred within 2 years in our study. Median time to recurrence was 9.1 months in the symptomatic cohort and 15.7 months in the surveillance cohort. Implementing a surveillance schedule with the combination of blood work and imaging over 2 years postoperatively wherein patients are at highest risk of recurrence would offer a balance between cost and benefit. The role of primary care practitioners in providing follow up after surgical resection and completion of adjuvant chemotherapy is also an important consideration in generating a consensus for surveillance (45-48).

The limitations of our study include those inherent to its retrospective design. Given the non-randomized, retrospective nature of this study, it is difficult to discern whether differences in ability to receive palliative chemotherapy between symptomatic and surveillance patients may also be related to differences in disease biology. However, our findings are consistent with the recent Netherlands-based observational cohort study (26). Our sample size was relatively small and limited to patients treated at one Canadian provincial cancer agency (across six BC Cancer sites). We were unable to determine the indications for all scans done postoperatively nor were we able to determine the presence or absence of symptoms or CA19-9 levels at the time of recurrence. We did not evaluate other patient factors such as preference, tolerance of adjuvant chemotherapy, and performance status upon completion of adjuvant therapy, all of which are clinical considerations in determining whether or not surveillance may be appropriate. Finally, we also acknowledge that despite the trend towards increased likelihood of receiving palliative chemotherapy in patients found to have recurrence

through surveillance scans, we are unable to determine whether or not receipt of palliative chemotherapy translates into improved outcomes.

To conclude, our study demonstrates that the majority of patients treated in BC underwent some form of surveillance imaging after the completion of surgery and adjuvant chemotherapy. Within the limits of our sample size, we demonstrate a trend towards increased likelihood of receiving palliative chemotherapy in patients found to have recurrence through surveillance as opposed to new onset symptoms. With the evolution of more efficacious palliative chemotherapy regimens, prospective studies to determine whether receipt of palliative chemotherapy in asymptomatic recurrences detected on imaging translates into improved survival and/or quality of life are warranted. The psychological impact of undergoing surveillance on patients' perception of care and anxiety regarding recurrence should also be evaluated.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by University of British Columbia Cancer Agency Research Ethics Board, H18-03243, and individual consent for this retrospective analysis was waived.

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