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Prevalence and significance of subcentimeter hepatic lesions in patients with localized pancreatic adenocarcinoma

Shereef M. Elnahal, BA^{a,*}, Atul B. Shinagare, MD^b, Jackie Szymonifka, MA^c, Theodore S. Hong, MD^d, Peter C. Enzinger, MD^e, and Harvey J. Mamon, MD, PhD^f

^aHarvard Medical School, Boston, Massachusetts

^bDepartment of Radiology, Brigham and Women's Hospital, Boston, Massachusetts

^cDepartment of Biostatistics, Massachusetts General Hospital, Boston, Massachusetts

^dDepartment of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts

^eDepartment of Medicine, Dana Farber Cancer Institute, Boston, Massachusetts

^fDepartment of Radiation Oncology, Brigham and Women's Hospital, Boston, Massachusetts

Abstract

Objectives—To determine the prevalence and significance of incidental hepatic and pulmonary sub-centimeter lesions in patients with localized pancreatic cancer.

Methods—This retrospective study included 101 patients treated for localized pancreatic adenocarcinoma from 1999 to 2007. Staging and follow-up imaging was reviewed to determine the frequency of sub-centimeter liver and pulmonary lesions. Using Cox regression, we calculated adjusted hazard ratios (HR) to determine the association between presence of liver and pulmonary lesions and overall survival.

Results—Forty patients (39.6%) had sub-centimeter hepatic or pulmonary lesions on staging scans. Of these patients, 33 (82.5% of patients with lesions) had eventual metastases in the same organ as the lesions. Of this group, seven patients (17.5% of patients with lesions) eventually had a metastasis at the site of the original lesion. Liver lesions predicted the occurrence of metastatic disease to the liver compared to patients without lesions (67.7% with lesions vs. 44.4% without, $p = .034$). Sub-centimeter liver lesions at diagnosis were significantly associated with reduced overall survival (HR 1.65, $p = 0.036$).

Conclusions—Sub-centimeter lesions in the liver and lung are common in patients with localized pancreatic cancer. The presence of indeterminate lesions may be associated with reduced overall survival.

*Corresponding author. Harvard Medical School, 6 Soldiers Field Park, Ste 307 Boston, MA 02163. shereef_elahal@hms.harvard.edu (S.M. Elnahal).

Conflicts of interest: None.

Introduction

Pancreatic cancer typically presents with locally advanced or metastatic disease, and is resectable in only 15–20% of patients¹. Because resection is the most effective treatment for this malignancy, it is particularly important to identify which patients are surgical candidates by radiographic staging¹. The staging process for patients with a new diagnosis of pancreatic cancer most typically involves CT of the chest, abdomen and pelvis in order to determine the local extension of the tumor and whether there are detectable distant metastases. Incidental lesions in the lung and liver are fairly common in the general population, and their detection during staging raises the specter of distant metastasis^{2,3,4}. These lesions may represent cysts, hamartomas, and hemangiomas in the liver and granulomatous lesions in the lung, in addition to foci of metastatic disease. Such lesions are often difficult to characterize by imaging and too small to target for biopsy. Therefore, they may confound determinations of resectability and assessments of overall prognosis.

Although studies exist which describe the significance and prevalence of incidental lesions in the liver and lung, little data is available regarding the significance of such findings in patients with documented malignancy. There is literature which characterizes the radiologic appearance and clinical significance of solitary pulmonary nodules (SPNs), and while the incidence in the general population is known, little data is available for patients with known malignancy⁵. Evidence-based management for SPNs has also been thoroughly developed for the general population, but not for subgroups of patients with small lesions and known malignancy. Similarly, the radiographic appearance, incidence, and significance of incidental findings in the liver have not been reliably documented for patients with pancreatic cancer. In sum, the significance of incidental lesions in the liver and lung has not been adequately studied in patients with pancreatic cancer, nor have any prognostic determinants been made related to their presence.

The purpose of this study was to determine the prevalence and prognostic significance of sub-centimeter hepatic and pulmonary lesions that are too small to characterize definitively in patients with a new diagnosis of pancreatic cancer.

Materials and Methods

Subjects

This IRB-approved retrospective study included 101 patients treated for pathologically-proven localized pancreatic adenocarcinoma at our institution from January 1999 to December 2007. These were consecutive patients who were treated with external beam radiation therapy. December of 2007 was chosen as a cut-off to achieve at least three years of follow-up for each patient. All patients with the above criteria were included. Patients with an imaging or pathologic diagnosis of metastatic disease during staging were excluded from this study.

Image analysis

We analyzed the staging CT scans for 89 patients and abdominal MRIs for 12 patients (the patients for whom we analyzed MRI scans either had no CT scan completed due to contrast

allergy, or did not have CT scans available in our records).. The radiology reports of initial staging studies were reviewed to identify the patients with sub-centimeter liver or pulmonary lesions that were either too small to characterize or otherwise equivocal. For these lesions, radiologists would often report their diagnostic impression (e.g., cystic, hemangioma, suspicious for metastatic disease), yet still deem the lesion to be of uncertain significance due to the sub-centimeter size. Any lesion with a definitive diagnosis (a diagnosis given without the stated caveat that the lesion was too small to characterize) by report was excluded from the analysis. One of our co-authors (AS), a radiologist, performed central review of the images and confirmed these sub-centimeter lesions. Follow-up imaging was reviewed to determine the outcome of the lesions. Lesions that remained unchanged after at least 12 months were considered benign. Lesions were classified as metastases if they progressively increased in size or developed characteristic imaging features of metastases, such as ring enhancement and washout. If a metastatic lesion was seen in the exact same anatomic location as the original sub-centimeter lesion, we considered the original lesion to represent metastatic disease. We determined the proportion of patients who developed metastatic disease in the same organ as the initial sub-centimeter lesions, as well as the proportion of sub-centimeter lesions which later proved to be metastases. Finally, all instances of distant recurrence to the liver and lung were recorded for each patient using radiologic reports, noting the date and location. All patients had at least one follow-up scan performed every six months. Using this information, we calculated the frequency of metastases to the liver and lung in patients without sub-centimeter lesions in those organs as a basis for comparison.

Clinical Parameters

We recorded baseline, pre-treatment clinical parameters for each patient in order to adjust for these variables in statistical comparisons between patients with sub-centimeter lesions and patients without. Clinical parameters for each patient were extracted from electronic medical records. Baseline tumor characteristics such as tumor size, vessel involvement, and abdominal lymphadenopathy were collected from radiologic reports of staging CT or MRI scans. We also obtained pathologic information such as the presence of lymphovascular invasion, perineural invasion, margin status, and tumor grade from pathology reports. Due to the relatively small number of patients with lung lesions of uncertain etiology, baseline characteristics were not compared between patients with lung lesions and those without. We also recorded the specific treatments that each patient received.

Date of death was also recorded for each patient, derived primarily from the Social Security Death Index⁶. This information was used to calculate hazard ratios for associations between lesions and overall survival.

Statistical Analysis

Chi squared tests were used to compare the frequency of categorical baseline characteristics and tumor pathology between all three groups of patients (total cohort, with liver lesions, without liver lesions), as well as associations between the presence of lesions and metastatic disease risk to the liver and lung. We used the Kruskal-Wallis test to compare medians of continuous variables between the groups. Univariate and multivariate Cox regression were

used to calculate hazard ratios, adjusting for all recorded clinical and tumor characteristics, as well as surgical findings (including resectability). Kaplan-Meier analysis was used to generate survival curves and comparisons were made using a stratified log-rank test. Due to the small number of patients with lung lesions, statistical associations and survival curves were not generated for this group of patients.

Results

Baseline Patient and Tumor Characteristics

Our study analyzed 101 patients with a new diagnosis of localized pancreatic adenocarcinoma. Baseline clinical parameters are presented in Table 1. Sixty-three patients (62.4%) did not have sub-centimeter liver lesions on initial staging and 31 patients (30.7%) did have single or multiple sub-centimeter lesions in the liver. As only 15 patients had equivocal lung lesions, statistical analyses were limited to patients with liver lesions. Gender, smoking habits, ECOG performance status, family history of pancreatic disease, CA 19-9, and other variables were not associated with the presence of liver lesions. Approximately half of the patients were considered resectable by imaging characteristics (Table 2). The median tumor size was 3.2 cm. Tumor resectability, tumor size, arterial and venous involvement, lymphovascular or perineural invasion by pathology, and surgical margin status were not associated with the existence of sub-centimeter lesions in the liver.

Treatment Characteristics and Surgical Findings

Seventy-three patients were explored for possible resection. Of this group, 49 patients were resected. Surgical findings are described in Table 3. All patients in our cohort received chemo-radiation. Seventy-four patients underwent chemotherapy either after chemo-radiation or post-operatively. Fifteen patients underwent surgery after radiation therapy; of this group, 8 patients were able to undergo a complete resection. Surgical treatment, tumor differentiation, pathologic T stage, and post-radiation treatments did not differ significantly between those with sub-centimeter hepatic lesions and those without.

Sub-centimeter Lesion Characteristics

A total of 40 patients (39.6% of total cohort) had either sub-centimeter hepatic or pulmonary lesions. For these lesions, radiologists provided a variety of initial impressions of the possible diagnosis, but could not definitively characterize them. The most common impression was cystic (29.0%), followed by hemangioma (22.6%) and lesions that appeared suspicious for metastatic disease (16.1%). The reports did not give an initial impression of the appearance of sub-centimeter lesions in 25% of patients who had them. Of the 49 patients with sub-centimeter lesions, 33 patients (82.5% of patients with lesions) had eventual metastases in the same organ by radiologic report, and seven patients (17.5% of patients with sub-centimeter lesions) were found to have metastases in the same exact location. These seven lesions were considered to be metastases on follow-up studies.

Of the 31 patients with liver lesions, 21 patients (67.7%) developed liver metastases and 5 patients (16.1%) developed confirmed metastases in the same location as the sub-centimeter lesions (Table 4). The overall rate of metastasis to the liver was significantly higher in

patients with sub-centimeter liver lesions than in patients without liver lesions (67.7% with lesions vs. 44.4% without, $p = .034$). Of the 15 patients with lung lesions, 6 patients (40.0%) developed lung metastases and 2 (13.3%) had confirmed metastases in the same location. The overall rate of metastases to the lung was not higher for patients with sub-centimeter lung lesions than for patients without such lesions (40% with lesions vs. 41.2% without, $p = .938$). Data regarding liver lesions was unavailable for 7 patients, and information regarding lung lesions was unavailable for 52 patients (no pre-treatment chest CT data was available by report for these patients).

Survival and Recurrence Outcomes

As expected, Kaplan-Meier analysis showed reduced overall survival for patients with a CA-19-9 of greater than 100 and for patients who were unresectable (Figure 1). Survival analysis showed reduced overall survival for patients with sub-centimeter liver lesions ($p = .027$). Univariate hazard ratio analysis showed also showed that sub-centimeter liver lesions at diagnosis was significantly associated with reduced overall survival for our patient cohort (HR 1.65, 95% CI 1.03 – 2.64, $p = .036$). This association retained significance on multivariate analysis (HR 1.75, 95% CI 1.05 – 2.94, $p = .034$). Statistical analyses for time-to-metastasis to specific organs (liver and lung) could not be performed due to inadequate power. The presence of pulmonary lesions was not associated with either reduced overall survival or worse distant control.

Discussion

In our cohort of patients, we found a high prevalence of sub-centimeter lesions in the liver and lung which were too small to characterize, approaching 40%. Overall, we found that about 18% of patients with such lesions were later confirmed to have metastases in those sites. In addition, we did find that patients with sub-centimeter liver lesions had a higher rate of metastasis to the liver than patients without such lesions. Given that we found that at least some of these sub-centimeter lesions were small foci of metastatic disease at diagnosis, the existence of the lesions may account for the significantly higher rate of liver metastasis that we observed over baseline. Finally, the presence of sub-centimeter lesions in the liver was associated with reduced overall survival, despite comparable patient and tumor characteristics between the group of patients with liver lesions and the group without.

While sub-centimeter lesions were quite common in our cohort of patients with pancreatic cancer, their appearance was variable and often ambiguous. This exemplifies the uncertainty surrounding these lesions during staging, particularly as to whether they represent metastatic disease that has yet to surface overtly. If confirmed in subsequent studies, our finding that sub-centimeter lesions in the liver are associated with an increased risk of metastatic disease to the liver and reduced overall survival could provide prognostic information to patients and clinicians. We did find that sub-centimeter lesions in the lung did not predict a greater occurrence of metastatic disease in the chest, indicating that this effect on overall survival, if true, is most likely conferred by lesions in the liver. Clinicians may use this information to consider following patients with sub-centimeter liver lesions more closely.

Few prior studies have investigated sub-centimeter lesions in patients with established malignancies, thus no data for pancreatic cancer is available for comparison. Ginsberg, et al. did examine the etiology of pulmonary nodules resected with video-assisted thorascopic surgery (VATS), and compared the findings between patients with established malignancy and previously healthy patients: their data supported a marginally increased risk of malignant etiology in patients with a prior cancer diagnosis⁷. Schwartz, et al. examined indeterminate liver lesions in patients with a variety of malignancies and found that 11.6% of them represented metastatic disease; however, pancreatic cancer was not well-represented in this cohort⁸. For breast cancer patients, Patterson, et al. found that 5% of patients with breast cancer had sub-centimeter liver lesions which developed into metastases and Khalil, et al. found that up to 97% of such lesions were benign⁹. Tan, et al. found that 4.3% of sub-centimeter liver lesions progressed in size in patients with rectal cancer¹⁰. Finally, in a recent study by Quyn, et al. investigating the significance of incidental pulmonary nodules in patients with rectal cancer, about 21% of lesions progressed to metastatic disease, a proportion similar to our finding. They did find that patients with more than four pulmonary lesions had worse rates of metastatic disease than patients with fewer lesions¹¹. The literature does seem to indicate that the outcomes of sub-centimeter liver lesions vary by type of cancer; therefore more studies investigating pancreatic cancer patients are needed to validate our findings.

There are important limitations to this study. We used radiology reports to initially identify patients with sub-centimeter hepatic or pulmonary lesions; therefore, our records are subject to inter-observer variability. Also, because many patients had staging chest x-rays instead of CT scans, or were initially scanned at outside hospitals, staging chest CT scans were unavailable for approximately half of the patients, limiting our analysis of pulmonary findings. We also had a relatively small number of patients, and for this reason, there was inadequate power to perform adjusted subgroup analyses. Next, we did run a large number of regressions in order to determine associations between clinical variables and prognostic outcomes, increasing the probability that associations could be found by chance. However, the number of analyses we performed was small enough to not require the use of correction methods (e.g., Bonferroni) commonly applied for large numbers of association tests. Also, we were limited in our ability to report metastatic disease risk due to the inconsistency of re-staging follow-up scans between patients: individuals who deteriorated clinically after metastasis and died without a documented follow-up scan, for example, would be missed by our study. Finally, the most important limitation is the retrospective nature of our analysis, limiting the ability to establish a causal relationship between the existence of sub-centimeter lesions and effects on overall survival or metastatic disease. Our conclusions, therefore, are hypothesis-generating by nature and need to be confirmed with prospective, matched-control studies.

To conclude, our data suggests that sub-centimeter liver and pulmonary lesions are common in patients with a new diagnosis of pancreatic adenocarcinoma, approaching a prevalence of 40%. Lesions in the liver predicted the occurrence of metastatic disease to that organ, while lesions in the lung did not. Finally, the presence of sub-centimeter lesions in the liver was associated with reduced overall survival. Prospective studies are needed to confirm our findings.

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Figure 1. Overall survival by pretreatment carbohydrate antigen (CA) 19-9 level (A) and resectability (B). All survival curves were generated using Kaplan-Meier analyses.

Figure 2. Overall Survival from Date of Radiation by Existence of Liver Lesions

Overall survival by the existence of liver lesions. All survival curves were generated using Kaplan-Meier analyses.

Table 1

Pre-Treatment Baseline Patient Characteristics

Characteristic	Total Cohort (N = 101)	Patients without Liver Lesions (N=63)	Patients with Liver Lesions (N=31)	p-value (chi2 or Kruskal-Wallis)
Patient Characteristics				
Median Age (years)	63.1	63.1	62.8	NS
Gender (male, %)	44.6	47.6	38.7	NS
Smoking (former or current, %)	62.8	61.7	63.3	NS
ECOG Status 1 (otherwise 0, %)	40.4	40.0	42.3	NS
Diabetes (%)	25.8	27.9	22.6	NS
Family History (pancreatic disease, %)	39.6	42.6	30.0	NS
Jaundice (%)	46.5	52.4	32.3	0.066
Stent (%)	46.4	45.9	45.2	NS
Weight loss, median (6 month, lbs.)	15.5	15.0	16.0	NS
CA 19-9, median	189.5	128.0	258.0	NS
CEA, median	2.1	2.5	1.8	NS

Table 2

Pre-Treatment Baseline Tumor Characteristics

Characteristic	Total Cohort (N = 101)	Patients without Liver Lesions (N=63)	Patients with Liver Lesions (N=31)	p-value (chi2 or Kruskal-Wallis)
Tumor characteristics				
Resectable (%)	48.5	47.6	45.1	NS
Tumor Size, median (CT or MRI, cm)	3.2	2.9	3.2	NS
Arterial Involvement (CT or MRI, %)	14.4	15.0	14.3	NS
Venous Involvement (CT or MRI, %)	38.9	33.3	53.6	NS
CT Lymphadenopathy (CT or MRI, %)	36.6	34.9	45.2	NS

Table 3

Surgical Findings

Finding		Total Cohort (N=49)	Patients without Liver Lesions	Patients with Liver Lesions	p-value (chi2)
% of resected					
T Stage	1	2.0	3.6	0	NS
	2	26.5	35.7	23.1	
	3	55.1	50.0	76.9	
	4	8.2	10.7	0	
N stage	0	40.8	41.9	35.7	NS
	1	59.2	58.1	64.3	
Tumor Grade	Well-differentiated	12.2	17.2	6.3	NS
	Moderately differentiated	55.1	48.3	56.3	
	Poorly differentiated	34.7	34.5	37.5	
Pathologic Features	Lymphovascular Invasion (%)	55.9	55.0	60.0	NS
	Perineural Invasion (%)	92.3	92.0	88.9	
	Positive Surgical Margin (%)	43.8	43.3	38.5	

Table 4

Metastasis rates by existence of sub-centimeter lesions

Liver lesions	N	Patients (%) with mets to liver	Patients (%) without mets to liver	p value (chi2)
Patients with sub-centimeter liver lesions	31	21 (67.7%)	10 (32.3%)	.034
Patients without sub-centimeter liver lesions	63	28 (44.4%)	35 (55.6%)	
Lung lesions		Patients (%) with mets to lung	Patients (%) without mets to lung	p value (chi2)
Patients with sub-centimeter lung lesions	15	6 (40.0%)	9 (60.0%)	NS
Patients without sub-centimeter lung lesions	34	14 (41.2%)	20 (58.8%)	