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Natural History of Patients with Subcentimeter Pulmonary Nodules Undergoing Hepatic Resection for Metastatic Colorectal Cancer

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Abstract

Background—Computed tomography (CT) imaging frequently detects subcentimeter pulmonary nodules (SPN) in patients undergoing resection of colorectal cancer liver metastases (CRCLM). Their clinical significance is unknown.

Methods—Patients were identified who underwent hepatic resection for CRCLM between 10/04 and 03/06. The presence and imaging features of preoperative SPN were analyzed for their association with progression-free survival (PFS), disease-specific survival (DSS), and SPN progression.

Results—160 patients underwent liver resection and 68 (43%) had SPN identified preoperatively. The median number of nodules was 1 (75th percentile: 2 nodules) and the median size of the largest was 3mm (25th–75th percentile: 2–5mm). SPN were unilateral in 77%, calcified in 19%, solid in 92%, and smooth in contour in 95% of patients. At a median follow-up of 31 months for survivors, SPN were proven to be metastatic disease in 35% of patients (24 of 68), either by radiographic increase in size or number (n=12) or histologic confirmation after resection (n=12). Median PFS for the 160 patients was 16 months and 3-year DSS was 78%. There was a trend towards a shorter median PFS in patients with preoperative SPN compared to patients with no SPN (12 versus 20 months; p=0.242). There was no difference in 3-yr DSS (70% versus 83%; p=0.46). SPN progression after hepatic resection did not significantly affect 3-yr DSS.

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Calcified nodules were less likely to progress compared to non-calcified nodules (8% versus 42%; $p=0.03$).

Conclusion—SPN are common among patients undergoing resection of CRCLM and approximately one-third of these will prove to be metastatic disease. The presence of limited preoperative SPN may be associated with shorter PFS after hepatectomy but does not significantly impact 3-year DSS, and should not necessarily preclude resection of hepatic metastases.

Introduction

Resection of hepatic colorectal cancer metastases, when feasible technically and in the appropriate clinical setting, is the standard of care. With improvements in perioperative outcome and systemic chemotherapy, the 5-year survival of patients with metastatic disease is reported to be 25% to 58%.^{1, 2} Modern preoperative evaluation typically includes a CT scan of the chest, abdomen, and pelvis to determine extent of disease prior to initiating an aggressive treatment regimen, that may include a partial hepatectomy. The utility of obtaining a routine chest CT scan in patients with a normal chest radiograph prior to performing hepatic resection for colorectal metastases has previously been questioned.³ However, the enhanced resolution of modern day multi-detector CT imaging has significantly improved the ability to identify not only hepatic metastases, but also sites of extra-hepatic disease in regional lymph nodes, peritoneum, and lungs. The presence of extra-hepatic disease introduces pause before proceeding with resectional therapy, as its presence has been associated with worse outcome.⁴

The enhanced resolution of thin-slice (5 mm) multi-detector CT imaging, although beneficial in many circumstances, has introduced a new clinical dilemma. Radiologists frequently report the presence of subcentimeter pulmonary nodules (SPN), which is not surprising given that the incidence of this finding in a healthy, general population can approach 25%.⁵ It can therefore be difficult to interpret these findings, and the significance of these SPN is particularly problematic in patients with known stage IV colorectal cancer. Whether these lesions represent metastatic disease, an evolving primary lung cancer, or a benign inflammatory process can ultimately affect outcome and thus may influence the decision to resect the liver metastases. Current management guidelines for performing further diagnostic tests on SPN, such as biopsy or excision, are directed at detecting early lung cancers.^{6, 7} Furthermore, the diagnostic tests themselves can be problematic, as SPN may fall below the threshold of detection for positron emission testing (PET) scans, fine-needle aspiration may not be feasible, they may be difficult to localize thoracoscopically, and the morbidity of a diagnostic thoracotomy seems unwarranted.

The aim of this study was to define the natural history and clinical significance of SPN in the context of patients with resectable hepatic colorectal cancer metastases. We also sought to describe the radiologic and clinical characteristics that best predict SPN progression after hepatic resection, thus confirming a diagnosis of metastatic pulmonary disease.

Methods

A prospectively maintained hepatobiliary surgery database at Memorial Sloan-Kettering Cancer Center (MSKCC) was reviewed for all patients with a diagnosis of colorectal cancer who underwent partial hepatectomy for metastatic disease between October 2004 and March 2006. Permission from MSKCC's Institutional Review Board was obtained prior to data review, and HIPAA compliance was ensured. This time period was chosen to include only patients who underwent thin-slice (5 mm) multi-detector CT imaging and to allow for adequate follow-up time postoperatively. Per standard protocol, patients underwent thin-slice CT imaging of their chest, abdomen, and pelvis every 3 months after undergoing hepatic resection, regardless of the presence of preoperative SPN. Preoperative and subsequent follow up CT scans that documented pulmonary nodules were re-examined by a single chest radiologist (MSG); the presence and imaging features of SPN on preoperative scans and changes over time were analyzed for their association with progression-free and disease-specific survival. SPN progression was defined as a documented radiographic increase in size or number of lesions or a histologic diagnosis of cancer, both of which satisfied diagnostic criteria of metastatic pulmonary disease. The CT scans of patients with no previous documentation of SPN were not reviewed. Patients with preoperative pulmonary nodules greater than 10 millimeters in size were excluded from analysis.

Radiologic characteristics of SPN were assessed with respect to number, size, and laterality. The largest nodule was further categorized based on the presence of calcification, a solid versus ground-glass appearance, and the contour of the lesion (spiculated, smooth, or lobular). When calcified and non-calcified nodules were present simultaneously, radiologic characterization was recorded for the non-calcified nodules.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 15.0 for Windows (SPSS, Inc. Chicago, IL). A combination of chi-square and Kaplan-Meier log-rank survival analysis was used to assess the association of the presence and progression of SPN with individual smoking history, site of primary disease (i.e. colon versus rectum), clinical risk score⁸, and survival. Logistic regression analysis was conducted to determine which clinical parameters and radiographic characteristics predicted SPN progression.

Results

Over the designated time period of October 2004 to March 2006, 164 patients underwent a partial hepatectomy for metastatic colorectal cancer. Four patients were excluded due to the presence of pulmonary nodules greater than 10mm in size, leaving 160 patients for analysis. The median age was 56 years (range 27 – 85) and 60% (n=95) were male. Median follow-up time was 31 months for survivors, at which time 73 patients (46%) had no evidence of disease, 59 (37%) were alive with disease, 27 (17%) had died from disease progression, and one patient died from an unrelated cause. CT scan images of patients with SPN, based on initial reports, were chosen for review; all scans were obtained within 4 weeks of surgery. In 11 of these cases, the re-review showed that SPN were in fact absent, and the patients were reclassified appropriately.

Subcentimeter Pulmonary Nodules (SPN)

Forty-three percent of all patients (68 of 160) had SPN present on their preoperative CT scan. There was no difference in the extent of hepatic resection, number of hepatic tumors, clinical risk score⁸, and administration of pre- and post-operative chemotherapy to patients with and without SPN on preoperative imaging (Table 1). There was no significant association between the presence of a preoperative SPN and positive smoking history. Likewise, the site of primary disease, i.e. colon versus rectum, was not significantly associated with the presence of SPN before hepatic resection.

Of the 68 patients with preoperative SPN, 49 underwent PET scan, 6 (12%) of which had fluorodeoxyglucose (FDG) avid lesion(s). Three of these six patients eventually underwent pulmonary nodule resection after hepatectomy, and all were histologically confirmed to be metastatic colorectal cancer. Two of the three remaining patients demonstrated SPN progression during follow-up with both eventually dying of progressive disease. There was no significant association between the finding of a positive PET scan and the administration of preoperative chemotherapy (7.7% vs 13.9%; $p=0.93$). Although 12 of 43 patients with negative PET scans did demonstrate SPN progression and 6 of these 12 patients had histologic confirmation of metastatic disease after resection, a positive PET scan had reasonable positive predictive value (83%) and was associated with SPN progression (83.3% vs 27.9%; $p=0.027$).

Radiologic Characteristics of SPN

Radiologic characteristics of SPN were recorded in 64 of the 68 patients with nodules. Complete chest CT images were not available for review in 4 patients; these 4 patients were excluded from analysis of imaging characteristics. The median number of nodules was 1 (75th percentile: 2 nodules) and the median size of the largest SPN was 3mm (25th–75th percentile: 2–5mm). SPN were unilateral in 77%, calcified in 19%, solid in 92%, and smooth in contour in 95% of patients (Table 2).

Predictors of SPN Progression

At a median follow up of 31 months for survivors, 35% of patients (24 of 68) ultimately demonstrated SPN progression and had their SPN proven to be metastatic disease based on radiologic changes ($n=12$) or histologic confirmation after resection with pulmonary metastatectomy ($n=12$). Radiologic changes included either an increase in size or number of pulmonary nodules. Logistic regression analysis was utilized to determine which radiologic nodule characteristics and clinical parameters predicted SPN progression. Based on univariate analysis, only the presence of calcification in the pulmonary nodule was associated with a lower likelihood of nodule progression (HR 0.12; 95% CI: 0.01 – 1.03; $p=0.05$; Table 3); only 1 of the 12 patients with calcified SPN demonstrated progression during follow-up. Thus, a multivariate model was not constructed. Nodule size, number, laterality, and contour were not associated with nodule progression. Only 3 patients had spiculated SPN and none had lobular nodules; none of the 3 spiculated lesions progressed during follow-up.

Using logistic regression analysis, the site of primary disease (i.e. colon versus rectum), a positive smoking history, and the number of hepatic tumors were not associated with SPN progression. The clinical risk score was calculated for each patient and then categorized into two groups to include patients with a score of 0, 1, or 2 (n=40) and patients with a score of 3, 4, or 5 (n=25). Complete parameter data was missing in 3 patients with preoperative SPN, and these patients could not be assigned a clinical risk score. Higher clinical risk score (3–5) was not associated with SPN progression after hepatectomy (Table 3). Similarly, by logistic regression analysis, none of the individual parameters that comprise the clinical risk score (listed in Table 1) were significantly associated with SPN progression. There was also no significant association of SPN progression after hepatic resection with whether or not the patient had received preoperative chemotherapy.

Survival Outcomes

Median progression-free survival (PFS) for the 160 patients was 16 months and 3-year disease-specific survival (DSS) was 78%. The median PFS for the group of patients with an elevated risk score (3–5) was significantly shorter compared to the group with a lower score (11 versus 22 months; $p=0.02$). Although the median DSS was not reached in either group, the 3-yr DSS was significantly lower in the group with the higher clinical risk score (68% versus 84%; $p=0.014$). None of the individual parameters that comprise the clinical risk score were significantly associated with DSS.

Patients with preoperative SPN (n=68) displayed a non-significant trend toward shorter median PFS compared to the 92 patients with no preoperative SPN (12 versus 20 months; $p=0.242$; Figure 1). There was no difference in 3-yr DSS (70% versus 83%; $p=0.46$; Figure 2). Among the patients with preoperative SPN, those with proven metastatic pulmonary disease (as evidenced by SPN progression during follow-up; n= 24), 3-yr DSS was not significantly different compared to those with no progression of SPN after hepatectomy (n=44; Figure 3).

Discussion

Nearly 50% of patients with colorectal cancer will develop metastases during their lifetime. Resection, in combination with chemotherapy, is the preferred modality of treatment for liver metastases. However, in the presence of extra-hepatic disease, there is a reduced benefit from hepatic resection.⁴ Interestingly, the actual site of extra-hepatic disease may affect long term outcomes differently, as pulmonary disease may not portend as bad an outcome as peritoneal or portal lymph node disease.⁹

In 1998, Povoski et al. questioned the utility of obtaining a routine chest CT scan prior to performing hepatic resection for colorectal metastases.³ In their study, a chest CT scan was obtained in 100 patients with a negative chest radiograph. Eleven patients were found to have a pulmonary nodule(s) and all 11 underwent pulmonary resection. Only 4 of these 11 patients were found to have malignant disease upon histologic review, one of which was a primary lung cancer, thus leading the authors to recommend only obtaining chest CT scans in patients with abnormal chest x-rays. Today, however, the typical preoperative work-up includes obtaining a preoperative CT scan of the chest, abdomen, and pelvis. As technologic

advances improve preoperative imaging, we now are identifying smaller foci of abnormalities and disease for which the clinical significance is unknown.⁵ Brent et al. recently reported that only 5 of 45 indeterminate lung lesions (11%) discovered on preoperative CT scans prior to primary colorectal tumor resection ultimately were found to harbor metastatic disease.¹⁰ Similarly, SPN are frequently detected, as high as 43% of the time as seen in our study, on preoperative CT scans of patients being considered for resection of colorectal liver metastases. It is often unclear whether these SPN represent metastatic disease, and if so, whether liver resection is the appropriate treatment. This report differs from others in that it describes the natural history and clinical significance of these SPN in the context of resectable hepatic colorectal metastases. It should be noted, however, that this study includes only those patients who were selected for hepatic resection and excludes patients with unresectable disease in whom the presence of SPN may potentially have a greater clinical significance.

The current recommendations and guidelines for managing SPN are largely derived from data directed at improving the early diagnosis of lung cancer.^{6, 11, 12} However, the patient population that presents with metastatic colorectal cancer does not necessarily represent a high risk population for lung cancer. Thus, the association with risk factors such as smoking history and occupational exposures that is highlighted in current guidelines for managing SPN does not necessarily apply to these patients. Indeed, we found no association with smoking history and the presence of SPN on preoperative imaging.

It is difficult to determine preoperatively whether a SPN represents a focus of metastatic disease. Also, it is unreasonable to routinely subject patients to attempts at biopsy or excision, particularly since the minority of these nodules actually represents metastatic disease and because their small size poses considerable technical challenges in obtaining an accurate biopsy.^{7, 13} In particular, fine-needle aspiration (FNA) and video-assisted thoroscopic surgery (VATS) techniques often are difficult and not feasible due to the small size of these nodules. Furthermore, routinely subjecting patients to the risks of general anesthesia for a VATS procedure is unwarranted given its low yield.

Positron emission tomography has been utilized to facilitate differentiating malignant from benign SPN, but the experience is limited and the results have been disappointing.¹⁴ There is likely minimal value of PET in lesions less than 5mm as this is below the threshold of resolution. For lesions between 5 and 10mm, a positive PET scan raises concern for malignancy, however, a negative result does not provide any clinically useful information due to the high possibility of a false negative result. In our study, 49 of the 68 patients with SPN had a preoperative PET scan. Five of the six patients that had a positive finding on PET scan demonstrated SPN progression during their follow-up period after hepatectomy and 3 eventually underwent SPN resection confirming metastatic disease. However, 12 other patients with SPN progression after hepatic resection initially had negative PET scan results. Thus, although a positive PET scan greatly raises the concern for metastatic disease, a negative PET scan does not definitively rule out the possibility of pulmonary spread.

In an effort to improve clinical interpretation of these SPN seen on preoperative imaging, we also determined if a patients' clinical risk score⁸ was associated with the presence of SPN or

its subsequent progression. Although an elevated clinical risk score, thus denoting higher risk, was associated with both a reduced progression-free survival (11 vs 22 months; $p=0.02$) and 3-yr disease-specific survival (68% vs 84%; $p=0.014$), we did not find any association of a high clinical risk score (3) with the presence of preoperative SPN. Furthermore, there was no association with the incidence of SPN progression, thus implying that an elevated clinical risk score did not help predict which SPN represented metastatic disease. Other clinical parameters, such as the primary site of tumor origin (colon vs rectum), a patient's smoking history, and the number of hepatic tumor metastases also did not predict which SPN were likely to progress (Table 3).

The radiographic appearance of a nodule may provide clues to the risk of malignancy. For example, a spiculated or ground-glass appearing lesion is more concerning for a primary lung cancer^{15, 16} while the presence of calcification suggests a benign etiology. In this study, preoperative CT scan images of those patients with a radiologic report stating the presence of SPN were reviewed with a dedicated thoracic radiologist (MSG) to further characterize the nodules. Eleven patients previously reported to have pulmonary nodules were deemed not to have any SPN on expert review and thus were recorded as such. This underscores the importance of an expert thoracic radiologist when trying to decipher the subtleties of a true SPN versus a pleural-based nodule. Ginsberg et al. have previously reported that in patients with a known malignancy, solitary nodules and nodules greater than or equal to 10mm were more likely to be malignant while nodules smaller than or equal to 5mm were usually benign.¹⁷ In our study, which is limited to only subcentimeter pulmonary nodules, we did not find any significant association between the number and size of the nodules and the incidence of nodule progression or histologic confirmation of a malignancy. It should be noted that 78% of the patients with preoperative SPN had only one or two nodules. Furthermore, the majority of SPN visualized in patients included in this study were characterized as solid and smooth in appearance; there were very few patients with spiculated or ground-glass lesions. Although limited by these small numbers, we found no association between the radiographic appearance of SPN and its subsequent progression. Only the presence of calcification in the SPN was associated with the nodule being of benign etiology.

Based on the above, it seems that it is very difficult to discern the significance of SPN from clinical parameters and radiologic characteristics. Given that the long-term survival of patients with metastatic colorectal cancer who undergo hepatic resection has dramatically improved over the last decade¹⁸, it naturally follows that as long as the presence of SPN does not portend a poor outcome, it should not necessarily prevent hepatic resection. Indeed, we found that although there was a trend towards reduced progression-free survival, there was no significant difference between patients who did and did not have SPN on preoperative imaging (12 versus 20 months; $p=0.242$; Figure 1). We also observed a similar 3-yr disease-specific survival between the two groups (70% vs 83%; $p=0.46$; Figure 2), suggesting that the presence of limited preoperative SPN should not necessarily preclude hepatic resection. As stated above, 78% of patients with preoperative SPN had only one or two nodules. The number of SPN was not associated with earlier progression or decreased survival in this study; however, it is conceivable that patients with multiple pulmonary nodules may indeed be at greater risk. Although one-third of patients with preoperative SPN

did progress in their lungs after undergoing hepatic resection, it seems that pulmonary disease may be a favorable recurrence pattern as evidenced by a similar 3-yr DSS compared to those patients with stable SPN (Figure 3). Of the 24 patients that demonstrated SPN progression, 12 of them underwent resection of their pulmonary nodules. While this may partially account for the similar 3-yr DSS observed between the 2 groups, it more likely represents a patient selection bias often encountered in retrospective studies, where patients have been carefully selected to undergo aggressive therapy. Nevertheless, this observation does underscore the importance of liver-directed therapy in the presence of low volume extrahepatic disease, but it by no means negates the potential negative impact of extrahepatic disease. As suggested by the survival curve in Figure 3, it is possible that survival would diverge after three years between patients with and without SPN progression, but given the length of follow-up in this study, we are unable to address this issue.

Conclusion

SPN are common among patients undergoing resection of hepatic colorectal cancer metastases and approximately one-third of these SPN will ultimately prove to be metastatic disease. Clinical parameters and radiologic characteristics provide minimal assistance in determining which SPN represent metastatic disease. Although the presence of a limited number of preoperative SPN may be associated with a shorter PFS after hepatectomy, it does not significantly impact 3-year DSS, and thus should not necessarily preclude resection of hepatic metastases.

REFERENCES

1. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004; 239:818–825. discussion 825–827. [PubMed: 15166961]
2. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg*. 2002; 236:397–406. discussion 406–407. [PubMed: 12368667]
3. Povoski SP, Fong Y, Sgouros SC, et al. Role of chest CT in patients with negative chest x-rays referred for hepatic colorectal metastases. *Ann Surg Oncol*. 1998; 5:9–15. [PubMed: 9524701]
4. Bennett JJ, Schmidt CR, Klimstra DS, et al. Perihepatic lymph node micrometastases impact outcome after partial hepatectomy for colorectal metastases. *Ann Surg Oncol*. 2008; 15:1130–1136. [PubMed: 18228106]
5. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet*. 1999; 354:99–105. [PubMed: 10408484]
6. Libby DM, Smith JP, Altorki NK, et al. Managing the small pulmonary nodule discovered by CT. *Chest*. 2004; 125:1522–1529. [PubMed: 15078769]
7. Daniel TM. A proposed diagnostic approach to the patient with the subcentimeter pulmonary nodule: techniques that facilitate video-assisted thoracic surgery excision. *Semin Thorac Cardiovasc Surg*. 2005; 17:115–122. [PubMed: 16087078]
8. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999; 230:309–318. discussion 318–321. [PubMed: 10493478]
9. Miller G, Biernacki P, Kemeny NE, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. *J Am Coll Surg*. 2007; 205:231–238. [PubMed: 17660069]

10. Brent A, Talbot R, Coyne J, et al. Should indeterminate lung lesions reported on staging CT scans influence the management of patients with colorectal cancer? *Colorectal Dis.* 2007; 9:816–818. [PubMed: 17931171]
11. Gould MK, Fletcher J, Iannettoni MD, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines. *Chest* (2nd edition). 2007; 132:108S–130S. [PubMed: 17873164]
12. Miller DL. Management of the subcentimeter pulmonary nodule. *Semin Thorac Cardiovasc Surg.* 2002; 14:281–285. [PubMed: 12232870]
13. Stiles BM, Altes TA, Jones DR, et al. Clinical experience with radiotracer-guided thorascopic biopsy of small, indeterminate lung nodules. *Ann Thorac Surg.* 2006; 82:1191–1196. discussion 1196–1197. [PubMed: 16996906]
14. Kernstine KH, Grannis FW Jr, Rotter AJ. Is there a role for PET in the evaluation of subcentimeter pulmonary nodules? *Semin Thorac Cardiovasc Surg.* 2005; 17:110–114. [PubMed: 16087077]
15. Tsuchiya R. Implication of the CT characteristics of subcentimeter pulmonary nodules. *Semin Thorac Cardiovasc Surg.* 2005; 17:107–109. [PubMed: 16087076]
16. Yoon HE, Fukuhara K, Michiura T, et al. Pulmonary nodules 10 mm or less in diameter with ground-glass opacity component detected by high-resolution computed tomography have a high possibility of malignancy. *Jpn J Thorac Cardiovasc Surg.* 2005; 53:22–28. [PubMed: 15724498]
17. Ginsberg MS, Griff SK, Go BD, et al. Pulmonary nodules resected at video-assisted thorascopic surgery: etiology in 426 patients. *Radiology.* 1999; 213:277–282. [PubMed: 10540672]
18. Kornprat P, Jarnagin WR, Gonen M, et al. Outcome after hepatectomy for multiple (four or more) colorectal metastases in the era of effective chemotherapy. *Ann Surg Oncol.* 2007; 14:1151–1160. [PubMed: 17195913]

Figure 1.

Progression-free survival of patients with subcentimeter pulmonary nodules present at the time of hepatic resection. Black line, no preoperative subcentimeter pulmonary nodules, n=92; dotted line, yes preoperative subcentimeter pulmonary nodules, n=68 (p=0.24).

Figure 2.

Disease-specific survival of patients with subcentimeter pulmonary nodules present at the time of hepatic resection. Black line, no preoperative subcentimeter pulmonary nodules, n=92; dotted line, yes preoperative subcentimeter pulmonary nodules, n=68 (p=0.46).

Figure 3. Disease-specific survival of patients with progression of subcentimeter pulmonary nodules after hepatic resection. Black line, no subcentimeter pulmonary nodule progression, n=44; dotted line, yes subcentimeter pulmonary nodule progression, n=24 (p=0.28).

Table 1

Disease and Operative Characteristics of 160 Patients With and Without Preoperative Subcentimeter Pulmonary Nodules Who Underwent Hepatic Resection for Metastatic Colorectal Cancer

Variable	(n=160)		p Value
	SPN (n=68)	No SPN (n=92)	
Site of primary disease			0.48
Colon	53 (78%)	66 (72%)	
Rectum	15 (22%)	26 (28%)	
Positive smoking history	36 (53%)	47 (51%)	0.94
Extent of hepatic resection			0.27
Minor (< 3 segments)	38 (56%)	52 (57%)	
Major (≥ 3 segments)	30 (44%)	40 (43%)	
Extrahepatic resection	25 (37%)	29 (32%)	0.24
Colon	9 (13%)	17 (19%)	
Periportal lymph nodes	10 (15%)	17 (19%)	
Diaphragm	6 (9%)	2 (2%)	
No. of hepatic tumors			0.052
Solitary	22 (32%)	42 (46%)	
2–3 Tumors	31 (46%)	25 (27%)	
4 Tumors	15 (22%)	25 (27%)	
Disease positive portal lymph nodes	1 (2%)	5 (5%)	0.40
Clinical risk score ⁸			
>1 Hepatic tumor	46 (68%)	50 (54%)	0.13
Hepatic tumor size > 5cm	10 (15%)	13 (14%)	0.99
CEA > 200 ng/mL*	3 (4%)	3 (3%)	0.99
Lymph node positive primary tumor	41 (60%)	55 (60%)	0.99
Disease free interval < 12 mo	48 (71%)	70 (76%)	0.55
Total score 0–2	40 (62%)	56 (64%)	
Total score 3–5	25 (38%)	31 (36%)	0.85
Chemotherapy			
Preoperative	49 (72%)	58 (63%)	0.30
Postoperative	61 (91%)	86 (94%)	0.79
FOLFOX regimen	48 (73%)	78 (85%)	0.10
FOLFIRI regimen	31 (47%)	47 (51%)	0.73

* Value not available for 8 patients.

Table 2

Radiologic Characteristics of Subcentimeter Pulmonary Nodules

Variable	(n=64)	
	n	%
No. of nodules		
1	35	55
2	15	23
3	5	8
4	4	6
5	1	2
>5	4	6
Size of largest nodule (mm)		
1	2	3
2	16	25
3	15	23
4	11	17
5	9	14
6	5	8
7	3	4
8	1	2
9	1	2
10	1	2
Bilateral	15	23
Calcified	12	19
Solid	59	92
Partly solid	0	0
Ground glass	5	8
Spiculated	3	5
Smooth	61	95
Lobular	0	0

Table 3

Regression Analysis for Predicting Subcentimeter Pulmonary Nodules Progression from Radiologic and Clinical Characteristics

Variable	(n=68)	
	Univariate logistic regression	
	HR (95% CI)	p Value
No. of nodules *	0.80 (0.53 – 1.20)	0.29
Size of largest nodule *	1.01 (0.77 – 1.32)	0.94
Bilateral *	0.86 (0.25 – 2.92)	0.81
Calcified *	0.12 (0.01 – 1.03)	0.05
Solid / partly solid / ground glass *	0.83 (0.13 – 5.36)	0.84
Spiculated / smooth / lobular	--	--
Rectal versus colon primary	0.38 (0.12 – 1.22)	0.10
Positive smoking history	0.38 (0.14 – 1.05)	0.63
No. of hepatic tumors	0.99 (0.71 – 1.38)	0.96
Elevated clinical risk score	1.04 (0.37 – 2.97)	0.94

* Analysis includes 64 patients for which adequate chest CT images were available for review.