ORIGINAL ARTICLE

How Uncommon are Isolated Lung Metastases in Colorectal Cancer? A Review from Database of 754 Patients Over 4 Years

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Abstract
Background It is commonly thought that colon cancer metastases to the lungs without involvement of the liver are rare.
Methods We performed a retrospective review of all patients with colorectal cancer diagnosed between December 2003 and August 2007 in Singapore. Isolated lung metastases were determined as (1) Definite if there was confirmed histology or cytology of the lung lesion(s) in the absence of liver lesions on CT scan, and (2) Probable if there were only radiological evidence suggestive of lung metastases rather than lung primary also in the absence of liver lesions on CT scan.
Results There were 196 patients with rectal and 558 patients with colon cancer (369 left-sided and 189 right-sided). There were 13 definite isolated lung metastases, and the remaining 43 were probable. Twenty-three (12%) patients with rectal cancer and 33 (6%) patients with colon cancer had isolated lung metastases (OR 2.11, 95% CI 1.21–3.70). Patients with $\geq$pT3 lesions (OR 1.92, 95% CI 0.75–4.93) and $\geq$pN1 (OR 1.56, 95% CI 0.86– 2.83) were more likely to have isolated lung metastases.
Conclusion The true incidence of isolated lung without liver metastases in colorectal cancer is likely to lie between 1.7% and 7.2%. While the incidence of isolated lung metastases is twice as common in patients with rectal cancer, it is still significant in patients with colon cancer. The absence of liver involvement should not preclude a search for lung metastases.

Introduction

The incidence of colorectal cancers is rising worldwide. Surgical resection is the primary treatment modality for colorectal cancers, and its outcome is most closely related to the extent of disease at presentation. However, metasta-

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ses are present in up to 30% of patients with colorectal cancers at the time of presentation.[1] The commonest sites of involvement are the regional lymph nodes, liver, lungs, and peritoneum.[2] Most deaths from cancer are still due to metastases.[2]

As the venous drainage of the colon is via the portal system, the first site of hematogenous spread of malignancy has always been regarded as the liver. But metastases bypassing the liver have been mentioned in several reports over the years, including to the lungs and thyroid.[3–6]

Lung metastases are seen in about 10–15% of all colorectal cancer metastases, but only 10% of these are isolated in the absence of liver metastases.[3,4] The higher incidence of this isolated lung metastases in rectal compared to colonic carcinoma was attributed to the direct hematogenous spread into the systemic circulation via the inferior and middle rectal veins, bypassing the portal venous system.[3,7]

However, colon cancer with isolated metastases not involving the liver is considered very rare with only a few

reports mentioning the existence of such an entity.[3,4] Our study aims to review the incidence of isolated lung metastases in all patients with colorectal cancers and to identify clinical factors that could be associated with this phenomenon.

Methods

Study Population

Tan Tock Seng Hospital is a single 1,300-bed hospital, the second largest in Singapore and provides secondary and tertiary medical care for about 1.5 million people. A retrospective review of the records of all patients diagnosed with colorectal cancers in our institution between December 2003 and August 2007 was performed. Data for this study was derived from a database of de-identified patient information.

Definition of Isolated Lung Metastases and Colon and Rectal Cancers

All patients with evidence of lung metastases without liver involvement were included in the review. Isolated lung metastases were determined as (1) Definite if there was confirmed histology or cytology of the lung lesion(s) in the absence of liver lesions on CT scan, and (2) Probable if there were only radiological evidence suggestive of lung metastases rather than lung primary also in the absence of liver lesions on CT scan. The findings on the CT scans were agreed upon by two independent radiologists. All scans were performed with intravenous contrast using a Siemens SOMATOM Sensation 64-slice CT scanner (Siemens AG, Wittelsbacherplatz, Muenchen, Germany) for the past 3 years.

Our institution's routine follow-up protocol for any patient with resected colorectal malignancy includes three monthly follow-up with CEA levels for the first 2 years and six monthly follow-up with CEA levels for the next 3 years with surveillance colonoscopy done 1 year after the surgery. CT scans of the abdomen and pelvis, and definitely thorax, is not routine and is only usually performed if there's a high index of suspicion or for monitoring of response of metastatic disease undergoing adjuvant therapy. Some of the histological features of the lung lesions that were suggestive of colorectal primary would include the presence of histological immunological markers such as Cytokeratin 20 (CK-20) and Villin, and in the absence of CK-7 and thyroid transcription factor 1 (TTF-1). Synchronous lung metastases were described as lesions arising within 6 months of the diagnosis of the primary, while metachronous metastases were lesions arising after 6 months.

We defined patients with rectal cancer in our study group as those located up to 15 cm from the anal verge excluding the rectosigmoid region. The location of the primary lesion in the colon cancer group commenced from the cecum until the rectosigmoid junction. These patients were also further subdivided into right- and left-sided lesions. Right-sided cancers were regarded if the primary was located from the cecum until the transverse colon, while left-sided cancers was located from the splenic flexure till the rectosigmoid junction.

Exclusion Criteria

Patients were excluded if there were any liver lesions suggestive of metastases within 6 months of diagnosis of the isolated lung metastases, but patients with liver metastases after 6 months from diagnosis of isolated lung metastases were included as it would indicate the progression of the dissemination of the malignancy. Patients were also excluded if the lung lesion(s) did not grow in the absence of adjuvant chemotherapy, indicating a higher probability that they were of infective or scar origins.

Statistical Analysis

For all the colorectal cancer patients reviewed for possible isolated lung metastases, differences in the age, gender, ethnic differences, and site of primary malignancy were tested using Chi square. Other association between the presence of isolated lung metastases and the tumor staging, nodal status of the resected specimens and the location of primary colonic lesions were also tested using Chi square. All results were presented with their Odds ratios (OR) and their 95% confidence interval (CI). All analyses were performed using the SPSS 13.0 statistical package (Chicago, IL, USA).

Results

There were 754 patients diagnosed with colorectal cancers in our institution from December 2003 until August 2007. Their mean age was 67.8 [standard deviation (SD) 12.6] years. A total of 196 (26.0%) patients had rectal cancers, while 558 (74.0%) had colon cancers, with 189 (25.1%) right-sided lesions and 369 (48.9%) left-sided ones. Table 1 illustrates the characteristics of all the 754 patients who had colorectal cancers.

Surgery was performed in 730 (96.8%) patients. The remaining 24 (3.2%) patients declined surgery. Emergency operation was performed in 181 patients (24.0%), and their indications were intestinal obstruction (133, 17.4%), bleeding (25, 3.3%), and perforation (25, 3.3). Details of the histology of the resected specimens are shown in Table 2.

Table 1 Characteristics of All 754 Patients who were Diagnosed with Colorectal Cancers

Characteristics	Results
Mean age (years)	67.8 (SD 12.6)
Gender	
Male	398 (52.8%)
Female	356 (47.2%)
Location of malignancy	
Right colon	189 (25.1%)
Caecum	41 (5.4%)
Ascending colon	54 (7.2%)
Hepatic flexure	36 (4.8%)
Transverse colon	58 (7.7%)
Left colon	369 (48.9%)
Splenic flexure	22 (2.9%)
Descending colon	59 (7.8%)
Sigmoid and rectosigmoid	288 (38.2%)
Rectum	196 (26.0%)

From the resected specimens, majority of the specimen showed an advanced T staging (T3/T4) in 83.6%, and positive nodal involvement (≥N1) in 54.8%, with a median of 17 (1–99) lymph nodes harvested. An overwhelming proportion of the malignancy were of moderate differentiation (n=679, 92.3%). Distant metastases was already present in 168 (22.3%) patients at presentation, with liver the most common organ involved in 15.0% (n=113). The median follow-up for all the patients was 21 (6–40) months.

There were a total of 56 patients with isolated lung metastases, 33 (59%) in patients with colon primary, and 23 (41%) in patients with rectal cancers. Of these 56 lung

Table 2 Histology of Resected Specimens

Tumor staging	
T1	33 (4.6%)
T2	84 (11.8%)
T3	405 (56.8%)
T4	191 (26.8%)
Median number of lymph nodes removed	17 (1–99 lymph nodes)
Nodal staging	
N0	322 (45.2%)
N1	214 (30.0%)
N2	177 (24.8%)
Grading of tumor specimen	
Well differentiated	26 (3.5%)
Moderately differentiated	679 (92.3%)
Poorly differentiated	31 (4.2%)
AJCC's classification staging	
I	79 (10.5%)
II	193 (25.6%)
III	289 (38.3%)
IV	168 (22.8%)
Number of patients with >1 metastases at diagnosis	32 (4.2%)

metastases, 13 (23.2%) were definite, (seven in colon cancers, six in rectal cancers) with the remaining 43 (76.8%) probable (26 in colon cancers, 17 in rectal cancers). Thirty (53.6%) patients had synchronous isolated lung metastases while the remaining 26 (46.4%) had metachronous lesions. The median time taken for isolated lung metastases to be diagnosed was 17 (4–36) months after diagnosis of the primary. Carcinoembryonic antigen (CEA levels) was only raised in 18 (32.1%) during follow-up. Table 3 shows the characteristics and details of the group of patients with isolated lung metastases.

Table 3 Characteristics of the 56 Patients with Isolated Lung Metastases

Characteristics	Results
Median age (years)	65 (23–88)
Gender	
Male	28 (50.0%)
Female	28 (50.0%)
Location of colorectal malignancy	
Colon	33 (58.9%)
Right-sided	8 (14.3%)
Left-sided	25 (44.6%)
Rectum	23 (41.1%)
Tumor staging of resected specimen	
T1	0 (0.0%)
T2	5 (8.9%)
T3	29 (51.8%)
T4	18 (32.1%)
Nodal status of resected specimen	
N0	18 (32.1%)
N1	23 (41.1%)
N2	11 (19.6%)
Diagnosis of isolated lung metastases	
Definite	13 (23.2%)
Colon	7 (12.5%)
Rectum	6 (10.7%)
Probable	43 (76.8%)
Colon	26 (46.4%)
Rectum	17 (30.4%)
CEA levels of patients performed when isolated lung metastases was diagnosed:	
When isolated lung metastases was diagnosed at presentation	20 (35.7%)
Raised	15 (26.8%)
Normal	5 (8.9%)
When isolated lung metastases was diagnosed during follow up	36 (64.3%)
Raised	18 (32.1%)
Normal	18 (32.1%)
Timing of isolated lung metastases	
Synchronous lesions	30 (53.6%)
Metachronous lesions	26 (46.4%)
Median time for diagnosis of isolated lung metastases after diagnosis of the primary (months)	17 (4–36)

In the 13 patients with definite diagnosis, eight had cytological confirmation, while five had histological evidence, of which four underwent wedge resection of their lung metastases, while one had a core biopsy of the lesion. In these 13 patients, details of the immunohistochemistry were present in seven, for which all were positive for CK-20 and Villin and negative for CK-7 and TTF-1. Of all the patients who underwent chest X-ray preoperatively or during follow-up, only eight (14.3%) patients had features suggestive of lung metastases, and all underwent CT scans of the thorax subsequently. In the group of patients with probable lung metastases, 27 had bilateral lung lesions, while 16 had unilateral nodules. Figure 1 summarised the above findings.

In the 33 patients with colonic primary, 13 had adjuvant chemotherapy, whereas in the 23 patients with rectal primary, four had neoadjuvant chemoradiation therapy, four had adjuvant radiotherapy, while nine have adjuvant chemotherapy.

Patients with rectal cancers were strongly associated with the presence of isolated lung metastases (OR 2.11, 95% CI 1.21–3.70, $p=0.011$) compared to colon cancer patients (Table 4). Analysis of the subgroup of patients with colonic primary showed that isolated lung metastases were slightly more commonly seen in left-sided colon cancers compared to right sided ones (OR 1.64, 95% CI 0.73–3.72, $p=0.260$; Table 5), though not statistically significant. More advanced T-staging, ≥T3 lesions (OR 2.44, 95% CI 0.57–10.43, $p=0.291$) seems to be associated with isolated lung metastases in colon cancers. Whereas in rectal cancers, the presence of nodal disease (OR 3.03, 95% CI 0.97–9.48, $p=0.055$) appears to be more strongly associated with isolated lung metastases (Table 6).

Discussion

Reports decades ago showed that pulmonary parenchyma metastases happened in about 10–15% of all colorectal cancers with an approximately 10% of these cases being isolated to the lung.[3,4] It has been reported that the lungs could be the only site of metastasis when the primary tumor is in the rectum, with incidence of up to 12%.[4,8,9] The high incidence of systemic recurrence in rectal carcinoma was attributed to direct spread into the systemic circulation via the inferior and middle rectal veins.[3,7,10]

The present series supports this hypothesis as those patients with rectal cancers were shown to have a much higher incidence of isolated pulmonary metastases than those with colon cancers: 12% vs. 6%, respectively. This sizeable percentage rate of isolated lung metastases in rectal cancers has a rather serious implication in its management. CT scans of the thorax should be routinely carried out for patients with rectal cancers for staging and surveillance since around half of these lesions in the present series occurred at diagnosis or within 6 months of presentation. This is especially so as reports have shown favorable long-term results even after repeated surgical resection for lung metastases from colorectal primaries.[11,12]

However, there has never been any postulation for the rationale associating colon cancer with isolated lung metastases, unlike that of rectal cancer. As the venous drainage of the colon is via the portal system, the first site of hematogenous spread of malignancy has always been regarded as the liver. But metastases bypassing the liver have been mentioned in several reports over the years, involving the lungs and/or thyroid only.[3–7] The incidence of isolated lung without liver metastases in colon cancer patients ranged from 1% to 3.8% and was only mentioned in a few reports over the decades[3,4] compared to 5.9% in the present series.

The precise mechanism accounting for this phenomenon of skip metastasis bypassing the first draining solid organ or the sentinel node through the hematogenous and lymphatics route is unclear. Various reports cite nonanatomic spread to any draining lymph node or solid organ and nonsequential spread within the lymphatic bed or hematogenous sites as possible explanations. These features could be related to the differences in tumor biology among various patients, tumor types, or even within a given tumor,[13–15] supporting the "seed and soil" hypothesis.

The authors feel that the increased presence of isolated lung metastases in patients with advanced T and N disease is not surprising and has been highlighted in other reports,[16–19] even though the result was statistically not significant. This tendency may perhaps reflect the increased likelihood of skipped metastases through nonanatomical, nonsequential channels after surgery for locally advanced tumors, for which further studies would be required. But isolated lung metastases also occurred in a significant proportion of patients with T2 and N0 disease. These features reinforced a heightened awareness at all times in detecting metastatic disease during the management of all
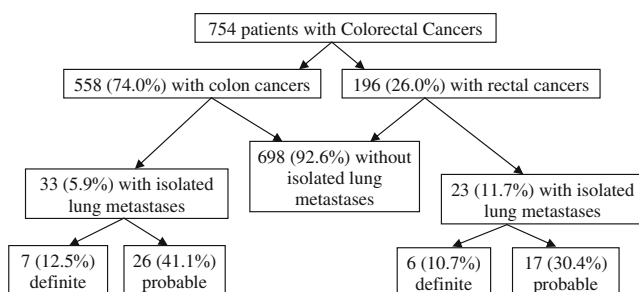
Figure 1 Flowchart describing the outcome of the 754 patients with reference to isolated lung metastases.

Table 4 Comparing Colon Ca Against Rectal Ca in Association with Isolated Lung Metastases

Variables	Absence of Isolated Lung Metastases	Presence of Isolated Lung Metastases	OR (95% CI) p value
Site of primary malignancy			
Colon	525	33	1.00
Rectal	173	23	2.11 (1.21 – 3.70)* p: 0.011

*p=0.011

patients with colorectal malignancy regardless of the stage of their primary cancers.

CEA has not been used as a screening test for detecting primary colorectal malignancy due to its insufficient specificity or sensitivity.[20] But its utilization as a tool to detect recurrent disease in patients following curative resection of colorectal cancers has been well documented.[21–24] However, in this current series, only half of the patients with isolated lung metastases were found to have elevated CEA levels during follow-up after initial curative surgery. This was not surprising, as CEA levels were shown to be especially useful in the detection of recurrent disease in the liver with sensitivity of up to 80%,

Table 6 Analysis of Variables for Isolated Lung Metastases in the Patients with Rectal Primary

Variables	Absence of Isolated Lung Metastases	Presence of Isolated Lung Metastases	OR (95% CI)
Age group			
≤65	83	11	1.00
≥66	90	12	1.01 (0.42–2.40) p=1.00
Gender			
Male	102	13	1.00
Female	71	10	1.11 (0.46 – 2.66) p=0.825
Tumor staging of resected specimen			
T1/T2	44	3	1.00
T3/T4	117	16	2.01 (0.56–7.22) p=0.409
Nodal status of resected specimen			
N0	69	4	1.00
N1/N2	91	16	3.03 (0.97–9.48) p=0.055

while CEA was much less reliable at predicting recurrent disease in other locations.[23,25,26]

Recent reports have recommended the regime of annual CT scan for the first 3 years after resection for AJCC stage

Table 5 Analysis of Variables for Isolated Lung Metastases in the Patients with Colonic Primary

Variables	Absence of Isolated Lung Metastases	Presence of Isolated Lung Metastases	OR (95% CI) p value
Age group			
≤65	197	16	1.00
≥66	328	17	0.64 (0.32–1.29) p=0.267
Gender			
Male	268	15	1.00
Female	257	18	1.25 (0.62–2.54) p=0.592
Location of malignancy in the colon			
Right Colon	181	8	1.00
Left Colon	344	25	1.64 (0.73–3.72) p=0.260
Comparing malignancy in the sigmoid colon versus rest of colon			
Sigmoid Colon	254	16	1.00
Rest of Colon	271	17	1.00 (0.49–2.01) p=1.00
Tumor staging of resected specimen			
T1/T2	68	2	1.00
T3/T4	432	31	2.44 (0.57–10.43) p=0.291
Nodal status of resected specimen			
N0	234	15	1.00
N1/N2	265	19	1.12 (0.56–2.25) p=0.859

II and III disease.[27,28] But neither the role of CT scan nor CEA can be used alone. Evaluation of each patient must include a thorough clinical evaluation, colonoscopy, CEA, and the necessary imaging modalities.[29,30]

All the above points brought out an important message in the current practice. As we tend to focus only on patients with stage III or high risk stage II disease during the follow-up with the aid of CEA levels, we may have already missed several patients with resectable metastatic disease. In view of the unpredictability of metastatic potential in each colorectal malignancy in every patient, the authors feel that the role of tumor genetic profiling may help to predict the outcome and hopefully prognosticate the disease in the future.

In our series, only four patients (7.1%) with isolated lung metastasis underwent metastasectomy, for which two are still alive currently (>3 years since the lung surgery), while the other two have passed away since. It has been shown in the literature that early diagnosis of colorectal pulmonary metastases is of paramount importance, as several reports have highlighted the survival benefits of pulmonary metastasectomy.[31–34] If the metastases could be completely removed, the cumulative 5- and 10-year (total) survival could be as high as 44% and 22%, respectively.

The majority of patients with isolated lung metastasis in our series were not suitable for resection due to several reasons. These included bilateral and multiple lung lesions, control of primary disease, inadequate pulmonary reserve after the planned resection, comorbid conditions, and patients' decisions. These are similar to the criteria mentioned in the literature of suitability for resection of pulmonary metastases.[31–34] After resection, improved survival was shown to be related to various factors such as smaller number and sizes of metastases, lower intrapulmonary tumor load, long disease-free interval, normal serum CEA level, and the absence of concomitant liver metastases and mediastinal lymph node spread. Pulmonary metastasectomy can even be performed effectively in patients with recurrent disease after prior hepatic resection for colorectal metastases, and prolonged survival can still be achieved.

As with most studies, there were several limitations in the present study. This series of patients was enrolled from a single institution, and the data was retrospectively reviewed. The small number of patients with isolated lung metastases may also mask several other important factors that could be accountable. Another significant point was that not all diagnosed lung metastases in this series were diagnosed through confirmed histology or cytology of the lung lesion(s). As such, some of the cases included may have had lung primaries or just post-infective lung scarring. We also do not use PET scan routinely, so some cases classified as isolated lung metastases may actually have other occult metastases as well. The fact that CT scan of the thorax was also not routinely performed for all patients was very significant, as it is possible that other patients with isolated lung metastases may be missed as a consequence, especially since rise in CEA was not present in half of the patients with isolated lung metastases during follow-up. Considering these limitations, the true incidence of isolated lung metastases may range from 3.1% to 11.7% in patients with rectal cancers, and from 1.3% to 5.9% in patients with colon cancers.

Although these limitations are significant, this study remains important in highlighting the presence and extent of isolated lung metastases in colorectal malignancy. It also attempted to identify factors that could aid in the detection of patients with isolated lung metastases earlier and perhaps allow proper interventions to be instituted.

Conclusion

The true incidence of isolated lung without liver metastases in colorectal cancer could lie between 1.7% and 7.2%. While the incidence of isolated lung metastases is twice as common in patients with rectal cancer, it is still significant in patients with colon cancer. Search for lung metastases should be included in the staging and surveillance of all patients with rectal cancer. The absence of liver involvement should not preclude a search for lung metastases.

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