Metastatic Tumors to the Colon and Rectum
A Multi-Institutional Study

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• Context.—Unlike the small bowel, the colorectal mucosa is seldom the site of metastatic disease.

Objective.—To determine the incidence of truly colorectal metastases, and subsequent clinicopathologic findings, in a substantial colorectal cancer population collected from 7 European centers.

Design.—During the last decade, 10 365 patients were identified as having colorectal malignant tumors, other than systemic diseases. Data collected included patient demographics, clinical symptoms, treatment, the presence of metastases in other sites, disease-free interval, follow-up, and overall survival. All secondary tumors resulting from direct invasion from malignant tumors of the contiguous organs were excluded, as well as those resulting from lymph node metastases or peritoneal seeding.

Results.—Only 35 patients were included (10 men) with a median age of 59 years. They presented with obstruction, bleeding, abdominal pain, or perforation. The leading source of metastases was the breast, followed by melanoma. Metastases were synchronous in 3 cases. The mean disease-free interval for the remaining cases was 6.61 years. Surgical resection was performed in 28 cases. Follow-up was available for 26 patients; all had died, with a mean survival time of 10.67 months (range, 1–41 months).

Conclusions.—Colorectal metastases are exceptional (0.338%) with the breast as a leading source of metastases; they still represent a late stage of disease and reflect a poor prognosis. Therefore, the pathologist should be alert for the possibility of secondary tumors when studying large bowel biopsies. Any therapy is usually palliative, but our results suggest that prolonged survival after surgery and complementary therapy can be obtained in some patients.


Unlike the small bowel, where secondary tumors are more common than the primary ones,1 the colorectal mucosa is seldom the site of metastatic disease. It may also be involved by direct invasion or extension from neighboring organs, intraperitoneal seeding, or intraluminal or intramural dissemination.

The most common mode of secondary involvement is by peritoneal seeding. Thus, it is much more common to see colonic involvement from intra-abdominal tumors such as ovarian carcinoma than those related to hematogenous metastases.

Virtually all primary cancers can lead to metastases in the colon and rectum, but the incidence of these metastases is not well documented. Berge and Lundberg’s2 10-year autopsy study from Malmo provides a rich source of data on such tumors because of the high rate of autopsies: 16 000 autopsies out of 26 000 deaths (62%). In their study, only 62 cases of colorectal metastases were found; the 2 primary sites were the lung (14 cases) and the breast (10 cases).

Conversely, there is a relative paucity of data concerning metastases to the colon and rectum during life. Previous reports are of individual cases3,4 or series from a single site.5,6 In their review of metastases of the digestive tract up to 1983, Caramella et al7 found only 265 cases of metastases to the colon and rectum; this number included all secondary tumors by either direct invasion, dissemination by (or from) peritoneal seeding, or hematogenous spread.

The present study was undertaken to determine the incidence of truly colorectal metastases and subsequent diagnostic findings, treatment, and clinical outcome in a substantial colorectal cancer population, collected from 7 institutions widely involved in the treatment of colorectal malignancy during the last decade.

MATERIALS AND METHODS

Seven hospitals contributed data to this study: St-Antoine, Cochin, and St-Joseph (Paris, France); Kremlin-Bicêtre (Kremlin-Bicêtre, France); Gustave Roussy (Villejuif, France); St-Luc (Brussels, Belgium); and Centre Vaudois (Lausanne, Switzerland). During the last decade, 10 365 patients were identified as having colorectal malignant tumors other than systemic disease (leukemia and lymphoma) in these centers.
Data collected included patient demographics (age, sex), clinical data (symptoms at presentation), site and size of tumor, treatment, presence of metastases in other sites, disease-free interval (DFI), follow-up, and overall survival.

Disease-free interval was defined as the interval from the treatment of primary tumor to the diagnosis of colorectal metastases. According to a study conducted by Kim et al. in 1998 related to the surgical treatment of clinically isolated adrenal metastases, when the DFI was less than 6 months, colorectal metastases were considered as synchronous. These authors found that poorer survival after surgical treatment of adrenal metastasis was observed in patients with a DFI less than 6 months. Consequently, they assumed that all metastases in those patients were probably synchronous, at least microscopically.

Overall survival was defined as the interval from the date of diagnosis of colorectal metastases to the date of last follow-up or death.

In order for a case to be included in this study, the patient had to have a lesion involving colorectal mucosa (or at least submucosa) and all the following criteria had to be met: the patient had a documented primary malignant tumor; colorectal metastases were confirmed by pathologic examination; histologic type of metastases was identical to that of the primary tumor, either by morphology or by immunohistochemistry; there was no other intra-abdominal or pelvic location, even peritoneal seeding or lymph node metastases.

Consequently, out of these 10,365 cases, all secondary tumors resulting from direct invasion from malignant tumors of the contiguous organs, such as ovaries (first surgery or second look), uterine cervix, or prostate, were excluded. Also excluded were patients with rectal involvement by gastric adenocarcinoma; histologic diagnosis of ‘poorly differentiated carcinoma’ without other specific information, even with a medical history of another malignant tumor; or carcinoma consistent with transitional cell carcinoma or other histologic type usually found in pelvic organs.

Colorectal synchronous metastases were included only when the primary tumor had a histologic type inconsistent with primary colorectal carcinoma and was located in a site not drained by the colorectal lymphatic system. Only 35 patients were included in this study.

### RESULTS

Patients were 10 men and 25 women, with a median age of 59 years (range, 30–81 years). Breast carcinoma was the most common primary tumor (n = 17), followed by melanoma (n = 7), sarcoma (n = 4), lung carcinoma (n = 4), renal cell carcinoma (n = 2), and Merkel cell carcinoma (n = 1). After excluding breast carcinoma, the male to female ratio was equal (9 men and 9 women). The majority of the tumors were adenocarcinoma (n = 18) followed by melanoma (n = 7). The pathology of metastasis was consistent with that of a primary tumor in all cases. Table 1 summarizes the number of metastases according to the histologic type and primary site.

Metastases were synchronous (DFI less than 6 months) in 3 cases: 2 cases had originated from the breast and 1 from the lung. The mean DFI for the remaining cases was 6.61 years (range, 6 months–19 years). Table 2 shows the DFI according to the histologic type. The longest DFI was for melanoma and the shortest one for kidney. The 2 other long DFIs (18 years) were observed for breast carcinoma.

Clinical presentation was available for 28 patients; all of them were symptomatic at the time of diagnosis. Thirteen patients presented with symptoms related to colorectal obstruction, 10 with bleeding, 4 with abdominal pain, and 1 with perforation. A preoperative biopsy was obtained in 16 patients. Biopsies were diagnostic of metastasis in 15 cases, but the diagnosis was missed as a primary tumor in the remaining biopsy. That patient had a history of pulmonary adenocarcinoma with DFI of 2 years.

The metastases were located in the right colon (10 cases), left colon (12 cases), transverse colon (9 cases), and rectum (3 cases). The metastases were diffuse in colorectal mucosa in only 1 case (breast lobular carcinoma). Surgical resection was performed in 28 cases; the metastases ranged in size from 2 to 8.5 cm (mean, 4.16 cm).

Grossly, the most common feature was a polypoid lesion (Figure 1a). Nodule, ulceration, and diffuse thickening walls were less common. Microscopic features were similar to those of the primary tumors (Figures 1b, c, and 3a). Immunohistochemistry was performed on the biopsy specimen, mainly for breast metastases (estrogens and progesterone receptors), leiomysarcoma (actin and desmin), and melanoma (S100 protein and Hmb45: Figures 1c, d, e, and 3a).

Complementary chemotherapy or radiotherapy was administered, sometimes with hormonotherapy. One patient benefited from anti–epidermal growth factor receptor drugs (lung carcinoma) and the treatment was only palliative in 3 cases.

All patients had a history of metastatic disease in extragastrointestinal sites: liver (9 cases), lungs (7), bone

<p>| Table 1. Number of Metastases According to the Histologic Type and Primary Sites |
|---------------------------------|--------------------------|---------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Histopathology</th>
<th>Subtype (No. of Cases)</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast adenocarcinoma</td>
<td>Adeno-K</td>
<td>Ductal (10)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lobular (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apocrine (1)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma</td>
<td>Skin (6)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Choroid (1)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>Squamous cell (2)</td>
<td>4</td>
</tr>
<tr>
<td>Bone and soft tissue</td>
<td>Osteosarcoma</td>
<td>Leiomysarcoma (2)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(1 thigh, 1 uterus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Clear cell carcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Merkel cell carcinoma</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<p>| Table 2. Disease-Free Interval (DFI) and Mean Survival Time According to Histologic Type |
|---------------------------------|--------------------------|---------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Primary Site</th>
<th>No. Cases</th>
<th>DFI, Mean (Range)</th>
<th>Survival, Mean (Range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast adenocarcinoma</td>
<td>12 (3 lobular)</td>
<td>7.56 y (1–18 y)</td>
<td>12.8 (1.5–41)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7 (1 choroid)</td>
<td>7.32 y (9 mo–19 y)</td>
<td>7.5 (1–21)</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>3</td>
<td>18 mo (0–24 mo)</td>
<td>8 (1–24)</td>
</tr>
<tr>
<td>Lung squamous</td>
<td>1</td>
<td>16 mo</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3</td>
<td>10.6 y (7–13 y)</td>
<td>14.6 (7–19)</td>
</tr>
</tbody>
</table>
Follow-up data were available for 26 patients. All had died from widely disseminated disease with a mean survival time of 10.67 months (range, 1–41 months). The shortest survival time was for melanoma, and the longest was for breast lobular carcinoma.

Table 2 shows the mean survival time according to the histologic type. The longest mean survival time (14.6 months) was for sarcoma but the number of cases (3) was too small to draw any conclusion. The other long mean survival time was for lobular carcinoma (17 months) with the same number of cases (3). The mean survival time for breast adenocarcinoma of any histologic type was 12.8 months.

Mean survival time was 12.35 months (range, 1.5–41 months) for the patients with surgical treatment and 9.8 months (range, 1–20 months) for the patients with nonsurgical management.

It is worth noting that one patient with colonic metastasis from lung carcinoma (adenocarcinoma) survived for as long as 24 months after surgery.

**COMMENT**

Data relating to metastases to the colon or rectum are sparse. Previous reports are of individual cases or small series from a single site. Our survey of the literature failed to yield any substantial series of patients from all primary sites during the life, and furthermore, we found no reference to long-term follow-up or outcome.

The pathogenesis of colorectal metastases involves different pathways. Direct invasion by a noncontiguous primary tumor along the fasciae and the mesenteric attachments is encountered during the course of pelvic cancers. An even more common pathway of tumor spread is via mesenteric reflections. Tumors of the gastrointestinal tract can gain access to the mesentery and ligaments when they break through the confines of their organs. Dissemination by peritoneal seeding occurs primarily in the pouch of Douglas. Involvement of the mesosigmoid and the right paracolic gutter is less frequent.

When colorectal invasions from another organ’s malignancy, through all these pathways and systemic malignancies (lymphoma and leukemia), are excluded, the truly colorectal metastases are exceptional. In this large series (10,365 patients) collected from 7 institutions widely involved in the treatment of colorectal malignancies, only 35 cases (0.338%) were identified as having true metastases to the colon and rectum. Unlike what has already been reported before in the largest autopsy series with the lung (14 cases) and the breast (10 cases) as a leading cause of metastases, the breast was the first primary site in our series (17 cases) with nearly 50% of cases. The frequency of colorectal metastasis from breast carcinoma, in a necropsy series, is reported to range from 8% to 12%, and in their series of a 15-year period, Taal et al. observed the same number as our study (17 patients) with breast carcinoma metastatic to the colon, rectum, or both. However, unlike the findings of these authors and others, there was no distinct predominance of the lobular type of breast carcinoma in our series. Only 3 out of 17 cases were of the lobular type, 13 cases were of the more common ductal carcinoma, and 1 was of the apocrine type.

In our series, the second source of colorectal metastases was melanoma, with 7 cases. In a series of digestive tract metastatic melanoma conducted by Adair et al., the small bowel outranked the large bowel by 4 to 1, and during 25 years only 2 out of 41 malignant melanomas involving the gastrointestinal tract were localized in the colon.
The predominance of breast and melanoma as a source of colorectal metastases in our series is probably due to the presence of 2 referral centers for the treatment of melanoma and breast cancer in 1 out of the 7 institutions that participated in this study (Gustave Roussy).

The lung was found to be the primary site in only 4 cases in our series. This is probably due to the fact that almost all these patients previously had colorectal surgery. The number of surgically diagnosed metastatic cases to the colorectum provided by some centers was far greater than the number of cases diagnosed only on biopsy without surgery. As lung metastases to the colon and rectum usually benefit from chemotherapy, we hypothesized that some metastases diagnosed only on biopsy in those centers were probably missed because of archival problems. Furthermore, except for the cases that presented with complications, lung carcinoma metastases to the colon and rectum during life are probably obscured by more serious metastases such as to the brain, bone, or liver.

Little is known about sarcoma metastasis to the colon and rectum; only single case reports exist in the literature. Four sarcomas were found in our series (2 osteosarcoma and 2 leiomyosarcoma) with long DFIIs. This number is expected to rise after the improved treatment and prognosis of sarcomas.

Mean DFI interval was equal between melanoma and breast carcinoma of all types (7.32 versus 7.56 years). The longest DFIIs (18 and 19 years) were also observed in patients diagnosed with these 2 histologic types (skin melanoma, shoulder; ductal breast adenocarcinoma). This interval was also long for sarcoma (10.6 years) but this information was available for only 3 patients.

Presenting symptoms of colorectal metastases are non-specific and difficult to distinguish from primary growth. They may present as abdominal pain, anorexia, vomiting, change in bowel habit, or obstruction. Our patients presented with symptoms related to intestinal obstruction, bleeding, or abdominal pain. Only one patient presented with perforation.

Even if the preoperative distinction between a primary and secondary colorectal neoplasm is almost impossible, the metastatic nature of the tumor was recognized after microscopic examination in all but one case in our series. In this case, the tumor was misdiagnosed on the biopsy as a primary tumor in a patient with a history of pulmonary adenocarcinoma after 2 years of follow-up.
The management of colorectal metastases depends on the presentation as emergency or chronic symptoms, preoperative diagnosis, and extent of dissemination. Only one patient in our series presented with perforation; she underwent surgical resection of colorectal metastases, as did 27 other patients. Only biopsy was performed in 7 patients, as the lesion was diffuse in 1 case, and a systemic therapy was thought to produce a favorable response in others (breast, 5 cases; lung, 1 case; sarcoma, 1 case; melanoma, 1 case; and kidney, 1 case). Mean survival time was 12.35 months (range, 1.5–41 months) for the first group and 9.8 months (range, 1–20 months) for the second group.

Surgical resection of metastatic tumors is controversial; it is expected that the question will arise further in the future, because of the recent improved prognosis of most malignant tumors, even though discrete, which allows the time for such metastases to appear at least histologically. Previous reports, focused on one primary site such as the breast, suggest that patients can survive for long periods after the discovery and treatment of colonic metastases. Hence, an increased awareness and earlier aggressive approach may improve the prognosis. Others have suggested that once the diagnosis has been made, except in emergency situations, systemic hormonal therapy, chemotherapy, or x-irradiation, either alone or as a complement to surgery, has produced a favorable response in more than half of patients concerned, thus avoiding surgical intervention.

In our study, no patient was still living 5 years after the diagnosis of colorectal metastases. The mean survival time was longer by only 3 months in patients with surgical treatment than in those without surgery (12.35 versus 9.8 months), but the number of patients in this series (especially those without surgery) is too small to draw a conclusion.

The rarity of colorectal metastasis makes a randomized prospective trial comparing surgery versus nonsurgical management highly unlikely. Even if the number of 35 patients is far from statistically significant to define reliable predictors of outcome, long-term survival up to 41 months was observed in one patient with breast carcinoma and 24 months for another one with lung carcinoma. Thus, we think that careful patient selection with primary site-controlled and complementary therapy may be associated with prolonged survival after surgical resection.

In conclusion, in this highly multi-institutional selected group of patients, truly metastatic tumors to the colon and rectum are exceptional (0.338%), with the breast as a leading source of metastases. Colorectal metastases usually represent the late stage of disease and reflect a poor prognosis. Therefore, even though they are exceptional, the pathologist should be alert for the possibility of metastatic tumors to the colon and rectum when studying large-bowel biopsies. The treatment is usually palliative, but our results suggest that careful patient selection with primary site-controlled and complementary therapy may be associated with prolonged survival after surgery.

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References