Metastatic pattern in colorectal cancer is strongly influenced by histological subtype

N. Hugen1*, C. J. H. van de Velde2, J. H. W. de Wilt1 & I. D. Nagtegaal3
1Department of Surgery, Radboud university medical center, Nijmegen; 2Department of Surgery, Leiden University Medical Center, Leiden; 3Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands

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Background: Clinical studies regarding colorectal cancer (CRC) have suggested differences in metastatic patterns between mucinous adenocarcinoma (MC), signet-ring cell carcinoma (SRCC) and the more common adenocarcinoma (AC). The current study systematically evaluates metastatic patterns of different histological subtypes in CRC patients and analyzes metastatic disease upon primary tumor localization.

Patients and methods: A nationwide retrospective review of pathological records of 5817 patients diagnosed with CRC who underwent an autopsy between 1991 and 2010 was performed. Patients were selected from the Dutch pathology registry (PALGA). To substantiate clinical relevance, metastatic patterns were compared with the prospective randomized multicenter Total Mesorectal Excision (TME) trial, which investigated efficacy of preoperative radiotherapy in rectal cancer patients.

Results: In the autopsy study, 1675 patients had metastatic disease. MC and SRCC patients more frequently had metastatic disease (33.9% and 61.2% versus 27.6%; P < 0.0001) and had metastases at multiple sites more often compared with AC patients (58.6% and 70.7% versus 49.9%; P = 0.001). AC predominantly metastasized to the liver, and MC and SRCC more frequently had peritoneal metastases. Metastatic patterns were also related to the primary tumor site, with a high rate of abdominal metastases in colon cancer patients, whereas rectal cancer patients more often had metastases at extra-abdominal sites. Results from the TME trial confirmed findings in rectal cancer patients from the autopsy study.
Conclusion: There are profound differences in metastatic patterns between histological subtypes and the localization of the primary tumor in CRC. Findings from this study should encourage to take these factors into account for follow-up strategies and future studies.

Key words: metastases, colorectal cancer, mucinous adenocarcinoma, signet-ring cell carcinoma

background

Despite the intensive follow-up for colorectal cancer (CRC) patients, metastatic disease still accounts for a high number of cancer-related deaths. At the time of presentation ~20% of patients has metastatic disease and 30%–40% of patients treated for potentially curable CRC relapses [1]. Large-scale autopsy studies have generated insight into metastatic patterns and demonstrated that different primary cancers metastasize to different sites with different frequencies [2]. CRCs most commonly metastasize to the liver, lung and peritoneum, but various other metastatic sites such as bone, spleen, brain and distant lymph nodes have been described [2–4]. Rare metastatic sites, such as pancreas and heart, are not well studied and generally only described in case reports.

Several clinical studies regarding CRC suggested that there are differences in metastatic patterns between histological subtypes. Mucinous adenocarcinoma (MC) represents 10%–15% of CRC and is considered a distinct clinical entity, with a predominant right-sided location and a poor prognosis in metastatic disease [5–7]. In follow-up of clinical trials, it was observed that MCs have a different distribution of metastatic disease, compared with the more common adenocarcinoma (AC) [5]. Signet-ring cell carcinoma (SRCC) is a relatively rare histological subtype of adenocarcinoma, present in 1% of CRC patients and is associated with a poor overall survival [6, 8, 9]. Population- and institution-based studies found extensive lymphatic and peritoneal spread in SRCC, suggesting a different biology [8].

Post-mortem studies offer a possibility to register both the extend and location of metastatic disease in different subtypes. Findings during autopsy may be considered the ultimate endpoint of disease. Most autopsy studies, however, have focused on metastatic patterns in one or more types of cancer, but have failed to address differentiating aspects such as histology within specific tumor subtypes.

This nationwide study evaluates the patterns of metastases in a large number of autopsies from patients with a history of CRC to generate insight into the relevance of histological subtype in the metastatic spread of CRC. To confirm the clinical relevance of our results, we also analyzed data from a prospective randomized multicenter trial [10].

methods and patients

A nationwide retrospective review of pathological and autopsy records of 5930 patients diagnosed with CRC and eventually autopsied between 1991 and 2010 was performed. Patients were selected from the Dutch pathology registry (PALGA) [11]. In the Netherlands postmortem examination is performed at the request of the family or treating doctor and is carried out by a pathologist. All autopsies included in this study were performed in order to obtain information on the medical status of the deceased or to determine the exact cause of death. No forensic autopsies were included. Undifferentiated tumors and tumors that were classified as carcinoids, neuro-endocrine tumors or other than adenocarcinoma ($n = 87$) were excluded. Furthermore, patients were excluded from the study if the location of the metastases could not be retrieved from the records ($n = 27$). Patient demographics (gender and age) were available for all cases, but information on cause of death or other clinical information was lacking in this database.

A total of 1679 patients with metastatic colorectal disease was identified. Tumor histology had been assessed by different pathologist in all cases. For this study, only MC, AC and SRCC were included. Local staging according to the TNM classification (5th edition of the American Joint Committee on Cancer) was reconstructed from the tumor extension described in the pathology or autopsy record. Metastases that were found within 6 months after surgery were considered synchronous. Tumors were classified as proximal if they were found in the cecum, ascending colon or transverse colon, and were classified as distal if they were found in the descending or sigmoid colon.

To confirm the clinical relevance of data from the autopsy study, we selected patients from the Total Mesorectal Excision (TME) trial. The design of the TME trial was reported previously [10]. This randomized multicenter study in the Netherlands included 1530 patients with primary resectable rectal cancer. Even though metastatic disease was an eligibility criterion, there were 88 patients with synchronous metastases. Patients underwent clinical examination every 3 months during the first year after surgery and annually thereafter for at least two more years. Examination during follow-up included liver imaging and endoscopy. When metastatic disease was detected, only the metastatic lesions present at that moment were registered. Metastases that developed subsequently were not registered.

statistical analysis

The $\chi^2$ test was used to compare demographics and tumor characteristics between the groups. All tests of significance were two-tailed: differences at $P$-values of <0.05 were considered to be significant. Statistical analyses were performed with the statistical software package SPSS 20.0 (SPSS, Inc., Chicago, IL, USA).

results

A total of 5817 autopsies was included in this study. AC was found in 4941 (84.9%) cases, compared with 809 MC (13.9%) and 67 SRCC (1.2%). The median age of all patients at death was 76 years (range 25–102). Metastatic disease was present in 1679 (28.9%) patients and was found in 27.6%, 33.9% and 61.2% of patients with AC, MC and SRCC, respectively ($P < 0.0001$). Clinicopathological data of metastatic CRC patients are presented in Table 1. The median time between surgery and autopsy was 28 months (range 7–246) in stage I, II
and III patients and 1 month (range 0–222) in stage IV patients. Patients who developed metastatic disease were diagnosed with an initial stage I tumor in 3.2% and 1.1% of AC and MC cases. None of the SRCC patients had stage I disease. In more than half of all patients, metastatic disease was synchronous with the primary tumor.

**distribution of metastases according to histology**

MC and SRCC patients more frequently had metastases at multiple sites (58.6% and 70.7%, versus 49.9% in AC, *P = 0.002*). Liver metastases were most frequent in both AC and MC patients (73.0% and 52.2%). In SRCC patients, more than half of all patients developed metastases on the peritoneal surface. Uncommon sites of metastatic diseases were brain, kidney, adrenal gland, ovary, heart, omentum, bone, pleura, pancreas and spleen.

There were major differences in metastatic patterns between histological subtypes (Figure 1a and supplementary Table S1, available at Annals of Oncology online). AC more frequently metastasized to the liver compared with MC and SRCC, 73.0% versus 52.2% and 31.7% (*P < 0.0001*). MC and SRCC metastases were more frequently found on the peritoneal surface, 48.2% and 51.2% respectively, compared with 20.1% in AC (*P < 0.0001*). Lung metastases were found in one-third of all cases, which was not different between the groups. SRCC markedly metastasized to distant lymph nodes more frequently, 43.9% compared with 22.3% and 19.9% in MC and AC, respectively (*P = 0.001*). These metastases were usually found adjacent to an organ with metastatic disease. Rare metastatic locations, such as heart, bone and pancreas, were found up to three times more frequently in SRCC than in MC or AC. Metastases to the ovary and skin or subcutaneous tissue were more common in SRCC and MC. Two autopsies on female patients reported a metastasis to the breast, both patients were diagnosed with SRCC.

**distribution of metastases according to primary tumor site**

Supplementary Table S2, available at Annals of Oncology online, and Figure 1b show metastatic patterns in relation to the primary tumor site. The frequency of liver metastases did not differ between colon and rectal cancer patients (69.6% versus 67.4%). Colon cancer patients presented more frequently with intra-abdominal metastases, such as peritoneal metastases (28.8% versus 16.1%, *P < 0.0001*), omental metastases (9.1% versus 2.9%, *P < 0.0001*) and ovarian metastases (3.2% versus 1.1%; *P = 0.019*). Rectal cancer patients, however, presented more frequently with extra-abdominal metastatic sites such as lung (42.0% versus 30.7%; *P < 0.0001*) and brain (5.0% versus 2.6%; *P = 0.014*). These findings were observed for both AC and MC patients even though not all sites reached statistical significance. In SRCC.
distribution of metastases according to tumor site. LN, lymph node. Figure 2 summarizes the most frequent combinations. AC Many patients developed metastatic disease at more than one combination of metastases. rectum could be identified within all three groups. However, no differences in patterns between colon and rectum could be identified (data not shown).

combination of metastases

Many patients developed metastatic disease at more than one site. Figure 2 summarizes the most frequent combinations. AC patients had the highest percentage of liver metastases, and suffered frequently from liver metastases as the only metastatic site. The occurrence of metastases exclusively to the liver was less common in MC and SRCC patients. Especially in SRCC patients, liver metastases were almost always observed in combination with other metastases. There were no differences in the frequencies of lung metastases, nor in the combinations of lung metastases with metastatic disease at other sites. Even though MC and SRCC patients suffered from peritoneal metastases more frequently, the proportion of peritoneal metastases only versus combinations with other metastases was equally distributed within all three groups.

clinical relevance: TME trial

There were 403 (31.1%) AC patients and 50 (32.7%) MC patients in the TME trial who developed metastatic disease (P = 0.398) during follow-up (median follow-up 11.6 years). There was only one SRCC patient in the study, who developed metastases in distant lymph nodes (both axillar and cervical) and on the peritoneal surface during follow-up. There were no differences in metastatic patterns between patients who were treated with or without preoperative radiotherapy (data not shown). In supplementary Table S3, available at Annals of Oncology online, and Figure 3, the distribution of metastases in rectal cancer patients from the TME trial and autopsy study is summarized. In the TME trial, liver metastases occurred more frequently in AC patients (59.6% versus 36.0%, P = 0.002), whereas peritoneal metastases were more common in MC patients (14.0% versus 4.5%, P = 0.005). This was comparable with the findings from the autopsy study. Frequencies of metastases at other sites were not significantly different in the TME trial.

discussion

This study is the first large-scale modern autopsy study for metastatic patterns in well-known subtypes of CRC. We show major differences in frequencies and combinations of metastatic sites between histological subtypes. These differences may have significant implications for clinical treatment, follow-up strategies and future clinical trials.

Compared with AC, the presence of metastatic disease in more than one location was more frequent in MC. Since curative surgery is an option mainly limited to liver metastases, this may explain the poor performance of MC patients in trials for metastatic disease [5, 12]. In MC patients, we found a high rate of peritoneal metastases. Several clinical studies already suggested differences in metastatic patterns between histological subtypes [5, 12, 13]. These studies also described a high number of peritoneal metastases in MC, with percentages varying from 22% to 45% [12, 13]. Peritoneal metastases are associated with a poor prognosis and survival is even worse if metastases in other organs are present [14]. Moreover, palliative chemotherapy in patients with peritoneal metastases is not very successful [15]. The high number of peritoneal metastases in MC is therefore another possible explanation for the poor survival in MC patients in advanced disease.

SRCC patients also presented more frequently with more than one metastatic site and an increased risk of peritoneal metastases. Interestingly, we found a high rate of distant lymph node metastases in SRCC. This enhanced lymphatic spread of SRCC has been noticed previously in small clinical studies [8]. SRCC patients showed a divergent pattern of metastases, with involvement of rare metastatic sites, such as heart, bone, pancreas and skin. Therefore, attention should be paid to uncommon findings on imaging in SRCC patients during clinical follow-up, since these may reflect metastatic disease.

Underlying mechanisms for differences in metastatic patterns between histological subtypes are not clear. Several studies have described molecular and biological differences between AC, MC and SRCC, contributing to a more aggressive biological behavior [16]. A theory behind the high number of peritoneal metastases...
in MC is that production of mucus under pressure allows cancers to gain access to the peritoneal cavity, through separation of tissue planes in the bowel wall and mucin-producing tumors may spread throughout the peritoneal cavity more easily in the form of gelatinous ascites [17, 18]. Moreover, fluid produced by MC tumors enhances uptake into regional lymph nodes, facilitating lymphatic spread throughout the body [17].

In this study, we also analyzed the differences in metastatic patterns between colon and rectal cancer. We show that both colon and rectal cancer predominantly metastasize to the liver. Moreover, colon cancer patients presented with abdominal metastases more often, whereas rectal cancer patients presented more frequently with extra-abdominal metastatic sites such as lung and brain. This was seen in both MC and AC patients, but not in SRCC patients. In the trial population, we confirmed the differences between rectal MC and AC regarding liver and peritoneal metastases, thus emphasizing the clinical relevance of our study data. The higher rate of metastatic lesions that was found in the autopsy study can be explained by the obvious reasons that only the first metastatic lesions were registered in the TME.

**Figure 2.** (A) Relative frequencies of combinations with liver metastases in AC, MC and SRCC patients, $P < 0.0001$. (B) Relative frequencies of combinations with lung metastases in AC, MC and SRCC patients, $P = 0.75$. (C). Relative frequencies of combinations with peritoneal metastases in AC, MC and SRCC patients, $P < 0.0001$.

**Figure 3.** Distribution of metastases in rectal cancer patients from the TME-trial and autopsy study. AC, adenocarcinoma, MC, mucinous adenocarcinoma, LN, lymph node. *$P \leq 0.05$, **$P \leq 0.01$, ****$P \leq 0.0001$. 

![Pie charts showing metastases](image-url)
trial and autopsy yields better detection of metastases. Studies that analyzed patterns of tumor recurrence and metastatic disease also found an increased risk of lung metastases in rectal cancer and found prognosis of lung metastases to be poor [19–21]. The higher rate of distant metastases in rectal cancer can be explained by the venous drainage of the rectum bypassing the liver straight into the inferior vena cava.

Knowledge of differences in metastatic patterns is important and may induce changes in clinical practice. A high rate of peritoneal carcinomatosis was found in MC and it has been advocated that all MC patients should undergo resection accompanied by perioperative intraperitoneal chemotherapy to improve survival [17]. The high number of peritoneal metastases in MC and SRCC should raise concern in case of tumor spillage and should possibly even result in adjuvant therapeutic measures. Insight into metastatic patterns may also impact the design of follow-up. Since liver and lung metastases are most common, regular imaging of chest and liver should be maintained. However, in case of unusual or indeterminate lesions, other imaging techniques such as PET-CT should be employed at an earlier stage, especially in MC and SRCC patients. Early detection of peritoneal metastases should be priority in these patient groups.

To our best knowledge this is the largest autopsy study focusing solely on metastatic disease from CRC. Furthermore, it is the first study that shows differences in metastatic pathways between histological subtypes in a large nationwide population. However, there are limitations due to the retrospective nature of this study. First of all, it is important to notice that an autopsy study unequivocally leads to a biased population, in which patients are included who have died postoperatively, had an unexpected clinical course, or died of other causes than CRC. Nevertheless, autopsy studies offer a unique opportunity to study the distribution of metastases and arguably can be seen as the gold standard in the study of cancer metastases. Secondly, it has not been possible to review the individual pathological diagnosis. Even though definitions of MC and SRCC have been standardized, variations in interpretation may have resulted in misclassification. However, the distribution of histological subtypes is similar to numbers reported in the literature [6, 7]. We also confirmed the clinical relevance of our findings with follow-up data of a phase III clinical trial. Even though the TME trial is a prospective trial, the numbers of metastatic lesions were lower, due to a more limited examination and registration compared with the autopsy study. This substantiates the importance of findings from autopsy studies. However, it may still be possible that there is an underestimation of the number of metastatic lesions in this autopsy study. Although we included only whole-body autopsies, metastatic lesions situated outside of the routinely examined regions may have been missed. Moreover, brain autopsy was not allowed for each patient. These limitations may have led to an underestimation of especially brain and bone metastases, but this bias potentially applies to all subgroups.

This study shows that histological subtype and primary tumor localization are important predictors of metastatic spread. MC and SRCC metastasize to different sites, in different combinations and are more likely to have a higher number of metastases. Furthermore, we show that colon and rectal cancers have different metastatic patterns as well. Based on profound differences in metastatic patterns between histological subtypes and localization of the primary tumor, we encourage to take these factors into account during preoperative examination for metastases and during follow-up. Our results also indicate that these factors should be considered a stratification factor in future research initiatives focusing on advanced disease.

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references

Clinical variables associated with PSA response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer


Departments of 1Medical Oncology and Haematology; 2Biostatistics, Princess Margaret Cancer Centre, Toronto, Canada; 3Prostate Cancer Targeted Therapy Group and Drug Development Unit, The Royal Marsden NHS Foundation Trust, Sutton, UK; 4Genitourinary Oncology Service, Meir Medical Center, Kfar-Saba, Israel

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Background: Abiraterone acetate (abiraterone) prolongs overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC). This study’s objective was to retrospectively identify factors associated with prostate-specific antigen (PSA) response to abiraterone and validate them in an independent cohort. We hypothesized that the neutrophil/lymphocyte ratio (NLR), thought to be an indirect manifestation of tumor-promoting inflammation, may be associated with response to abiraterone.

Patients and methods: All patients receiving abiraterone at the Princess Margaret (PM) Cancer Centre up to March 2013 were reviewed. The primary end point was confirmed PSA response defined as PSA decline ≥50% below baseline maintained for ≥3 weeks. Potential factors associated with PSA response were analyzed using univariate and multivariable analyses to generate a score, which was then evaluated in an independent cohort from Royal Marsden (RM) NHS foundation.

Results: A confirmed PSA response was observed in 44 out of 108 assessable patients (41%, 95% confidence interval 31%–50%). In univariate analysis, lower pre-abiraterone baseline levels of lactate dehydrogenase, an NLR ≤5 and restricted metastatic spread to either bone or lymph nodes were each associated with PSA response. In multivariable analysis, only low NLR and restricted metastatic spread remained statistically significant. A score derived as the sum of these two categorical variables was associated with response to abiraterone (P = 0.007). Logistic regression analysis on an independent validation cohort of 245 patients verified that this score was associated with response to abiraterone (P = 0.003). It was also associated with OS in an exploratory analysis.

Conclusions: A composite score of baseline NLR and extent of metastatic spread is associated with PSA response to abiraterone and OS. Our data may help understand the role of systemic inflammation in mCRPC and warrant further research.

Key words: prostate cancer, abiraterone acetate, NLR, mCRPC, response

†These authors contributed equally to this work.