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Review Article

Systematic review: Incidence, risk factors, survival and treatment of bone metastases from colorectal cancer

Troels Dreier Christensen*, Sandra Galinska Jensen, Finn Ole Larsen, Dorte Lisbet Nielsen

Department of Oncology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark

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ABSTRACT

Background: Bones are not considered a frequent metastatic site in patients with colorectal cancer (CRC). The purpose of the present study was to determine the incidence of bone metastases (BM) in CRC, to identify possible risk factors for BM, survival after BM, and effect of treatment of BM including antiresorptive treatment.
Material and methods: A computer-based literature search was carried out using PubMed and EMBASE.
Results: We included 29 studies. One randomized placebo controlled trial (RCT) study, two autopsy studies, five register studies, and twenty retrospective cohort studies. The studies described different cohorts making direct comparison difficult. Three studies analysed the effect of different treatments for BM including one RCT study.
Conclusion: The incidence of bone metastases was 3–7% in patients with CRC, and it was not possible to detect an increase in incidence over time. The most well established risk factors for BM are rectal cancer, having lymph node invasion at surgery of primary tumor, and lung metastases at any time. Other risk factors such as *RAS* mutation status have been suggested but results are not conclusive. Survival ranges from 5 to 21 months after diagnosis of BM depending on cohort, with survival of about 8 months in unselected patients. Several variables have been suggested as potential prognostic markers but are all poorly investigated. Treatment of BM is not well investigated, though patients seem to benefit from bisphosphonate treatment with regard to lower risk of skeletal related events. This review highlights the need for new research in the area.

1. Background

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with an estimated 1.4 million cases worldwide. In 2012 metastatic CRC (mCRC) was the cause of death in 693,900 patients [1], despite the advantages in screening, diagnosis and improved surgical and medical treatments.

About 20% of patients with CRC have already distant metastases at presentation [2] and totally 50% of patients with CRC will develop metastatic disease [3]. Moreover, a recent Norwegian study showed that 15.6% patients with CRC, who were considered surgically cured, had recurrent cancers including distant metastases during a five year follow up [4].

Today little is known about bone metastases (BM) from CRC. BM are considered frequent among patients with breast cancer, prostate cancer and lung cancer [5]. Bones are in fact the most frequent metastatic site among patients with breast cancer since up to 70% of all patients with disseminated breast cancer develop BM [6]. In breast, prostate and lung cancer, the antiresorptive treatment, bisphosphonates and denosumab, reduces further progression in bones and prevents complications by reducing the upregulated osteoclast activity caused by the metastasis. The outcome is fewer skeletal related events (SRE), and in the long term the antiresorptive treatment has an analgesic effect [7–10].

Since the relative survival of CRC has increased over the recent decades [11], we expect to see an increasing number of patients in our clinical practice with BM from CRC. For that reason, basic knowledge of the incidence, possible risk factors, survival and treatment of BM from CRC is essential, hence this review was made.

2. Method

In order to systematically review the literature about BM from CRC we completed the following search in PubMed on the 24th of September 2017 which resulted in 1064 hits: (((Bone AND metastases)) OR ("Neoplasm Metastasis"[Mesh] AND Bone)) OR (("Neoplasm Metastasis"[Mesh]) AND ("Bone and Bones"[Mesh]))) OR "bone metastases") OR "bone metastasis")) AND ((((("rectal cancer") OR "colon cancer") OR "colorectal cancer") OR "Colorectal Neoplasms"[Mesh]).

* Corresponding author.
E-mail addresses: troels.dreier.christensen.01@regionh.dk (T.D. Christensen), Sandragalinska@gmail.com (S.G. Jensen), finn.ole.larsen@regionh.dk (F.O. Larsen), dorte.nielsen.01@regionh.dk (D.L. Nielsen).

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The following search was performed in EMBASE on 18th November 2017 resulting in 1374 hits: ((rectum cancer or rectum tumor or rectum carcinoma or colorectal cancer or colon carcinoma or colon tumor or colon cancer) and bone metastasis).

To ensure a complete search we also searched for “Metastatic pattern AND ((((("rectal cancer") OR "colon cancer") OR "colorectal cancer") OR "Colorectal Neoplasms"[Mesh])” in PubMed (1013 hits) and ((Rectum cancer or rectum tumor or rectum carcinoma or colorectal cancer or colon carcinoma or colon tumor or colon cancer) and metastatic pattern) in EMBASE (52 hits).

The searches were last updated 2nd July 2018.

Furthermore, we searched reference list of relevant studies.

We included human studies written in English describing patients with BM from CRC. The studies should include at least 10 patients with BM from CRC. Reviews, case stories and studies published before 1975 were excluded. In total 29 studies were identified through our search of the literature [12–40].

The following information was extracted; incidence of BM, survival after BM diagnosis, treatment of BM and follow-up. If the authors did not display the incidence, we calculated it by dividing the number of patients with BM with the number of patients with CRC.

Furthermore, results of any statistical analysis regarding risk factors for developing BM, risk factors for poor survival after BM, and treatment efficacy were extracted.

3. Results and discussion

We included 29 studies (Table 1). One study was a randomized placebo controlled trial (RCT) [40], two were autopsy studies [38,39], five were register studies [33–37]. Twenty-one were retrospective cohort studies [12–32]. Six studies included unselected cohorts of patients with CRC [12–15,33,34]. The remaining studies included various cohorts of patients, for example cohorts only including patients with mCRC, CRC patients who underwent surgery, patients with adenocarcinoma or only rectal cancer patients [1–32,35-40]. Furthermore, most studies did not report the exact follow-up period and those that did had different follow-up periods. This made a direct comparison across studies difficult and interpretation of results challenging.

3.1. Incidence of BM

Twenty-seven of the studies reported an incidence of BM among their patients. The incidence of BM among the various subpopulations of CRC patients is presented in Table 1.

The incidence of BM in unselected patients with CRC was described in three retrospective cohort studies [13–15] and two large register studies [33,34] and ranged from 2.9% to 6.6%. The distribution of stage and exact follow-up period in these studies were not accounted for. A sixth study followed all patients until death, but unfortunately, they did not provide an exact incidence. However, they stated that 264 patients among more than 2500 patients developed BM giving an incidence around 10% [12]. As expected a higher incidence of BM was generally found when only including patients with mCRC. Two cohort studies described an incidence of BM of 7% and 6.9% among these patients [26,27] and the register study by Riihimaki et al. reported an incidence of 9.3% [34] A fourth study presented an incidence of 10.4% in a population of patients with mCRC adenocarcinoma [28]. Most of the studies might have underestimated the true incidence. Firstly, most studies did not report the exact follow-up period, and only one study reported that they followed patients until death. Secondly, all studies were retrospective or register based and mostly based on routine follow-up schemes, which not necessarily would capture asymptomatic BM.

Two autopsy studies also presented an incidence of BM among patients with CRC ranging from 1.7% in a study by Hugen et al. [38] to 23% in a study by Katoh et al. [39]. However, in both studies there was a potential heavy selection bias since autopsies were not described as being performed on all patients but only after request from doctors or patients. Therefore, these results should be interpreted with caution.

It has been suggested that the incidence of BM from CRC is increasing due to better diagnostics options and CRC patients living longer, but so far this has remained as speculations. In this review we were not able to assess if the incidence varied over time, due to differences in patient populations and overlap in time periods for data collection in the included studies.

3.2. Risk factors for BM

Fifteen studies described a statistical analysis of potential risk factors for BM [12,15,16,18,19,22,25,28,30–32,34,35,38,39]. Summary of their results is presented in Table 2. All studies were retrospective and they described different cohorts making comparison of the results difficult.

3.2.1. Primary tumor location

From the studies included in this review it seems likely that location of primary tumor affects the likelihood of BM, with an increasing risk of BM the more distal the tumor is located.

Eight out of twelve studies that compared the risk of BM among rectal and colon cancer patients [16,19,22,25,28,30,34,35] identified an increased risk among patients with rectal cancer, and none of the four remaining reported the reverse association [12,32,38,39]. Five studies presented results of multivariable analysis and in all studies rectal cancer was identified as an independent risk factor for BM [15,16,19,22,34]. The OR for BM among patients with rectal cancer compared to colon cancer was on multivariable analysis 1.5 (CI 95% = 1.4–1.7) in a large register study by Riihimäki et al. [34], and between 2.0 and 2.4 in three retrospective cohort studies [15,19,22]. Sundermeyer et al. did only report p values from their multivariable analysis [28].

The specific location colon or rectum might also affect the risk of BM. A study by Chiang et al. which only included patients with rectal cancer, identified an increased incidence of BM in distal rectum (11.11%), compared to the middle rectum (6.95%) and in the proximal rectum (3.44%) ($p < 0.001$) [25]. A similar result among colon cancer patients was observed by Riihimäki et al. [34]. They identified an OR for developing BM of 1.2 (CI 95% = 1.1–1.4) for patients with distal colon cancer opposed to proximal cancer.

A potential bias of the result could be that direct invasion of the bone was included as bone metastases, none of the studies reported that they excluded direct invasion in their analysis. The pattern of metastases could be explained by Batson's venous plexus, a network of valveless veins that connect the deep pelvic and thoracic veins to the internal vertebral venous system [20,30,39,41].

3.2.2. Primary tumor stage

No firm conclusions can be made regarding potential association between primary tumor stage and risk of BM. A study by Sundemeyer et al. conducted on mCRC patients, found a significant association between incidence of BM and early stage cancer on multivariable analysis [28].

Oppositely, Sun et al. and Zhenghong et al. identified a significantly increasing incidence of BM with increasing stage in univariate but not multivariate analysis. Both also included patients with CRC who did not developed metastases, and therefore the association found on univariate analysis most likely reflects the increased risk of all metastases in higher stages [15,19]. Oppositely, two cohort studies found no association [12,16].

3.2.3. Histological type of CRC and mutation status

Results regarding primary tumor grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated) and