Capecitabine Plus Bevacizumab for Cardiac Metastasis of Sigmoid Colon Cancer: Case Report and Literature Review

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Abstract. Background/Aim: Right ventricular cardiac metastasis from colorectal cancer (CRC) is rare and clinically silent. There is no standardised treatment. To date, only twelve cases have been reported in the literature. This is a case report and literature review of right ventricular cardiac metastasis from CRC. Case Report: A 75-year-old woman with a history of CRC treated with sigmoidectomy followed by liver and lung metastasectomy presented with a right ventricle tumour. Biopsy showed metastatic adenocarcinoma not suitable for resection because multiple lung metastases coexisted. The metastases were controlled for a prolonged duration by chemotherapy with capecitabine plus bevacizumab. According to the review of 13 cases, the median age of metastatic CRC that involves the right ventricle is 71 years and the primary site is half the colon and rectum. Half of cases have non-cardiac metastases at cardiac metastasis diagnosis. Chemotherapy is more suitable than resection in cases with metastases other than heart because resection of the right ventricle has a high risk. Conclusion: Cardiac right ventricular metastasis from CRC can be controlled by capecitabine plus bevacizumab.

Metastases from colorectal cancer (CRC) can occur either by lymphatic or hematogenous spreading, and the sites most commonly involved are the lymph nodes, liver, and lung.

Cardiac metastasis from CRC is an extremely rare event and the incidence is probably underestimated. A large autopsy series reported that colon carcinoma metastases to the heart account for 1.2%, with a prevalence of 2% of all metastatic neoplasms (1). The reasons for the limited number of reported cases are that cardiac tumours are usually asymptomatic and do not present themselves. A progressive metastatic mass of the heart occasionally causes acute heart failure or superior vena cava syndrome, resulting in sudden death (2, 3). Such masses are often associated with non-specific symptoms, including those of right-sided heart failure, dyspnoea, arrhythmias, pulmonary thromboembolism, and tumour thrombus (4). With regard to the frequency of cardiac metastases from any malignancy, the epicardium (75.5%), followed by the myocardium (38.2%) and endocardium (15.5%) has been reported to be involved (5). In this report, cardiac metastasis refers to the involvement of parts other than the epicardium. Herein, we present a case of a patient with right ventricular cardiac metastasis from adenocarcinoma of the sigmoid colon who was effectively treated with chemotherapy and review reports to date regarding CRC metastases to the right ventricle of the heart, their diagnosis, treatments, and prognosis.

Case Report

In July 2013, a 70-year-old woman underwent sigmoidectomy for moderately differentiated adenocarcinoma with wild-type RAS/BRAF. The presurgical radiological staging was deemed negative for distant metastases. The pathological stage was pT3N0M0 (stage IIA). The patient did not receive adjuvant therapy and entered the following scheduled clinical follow-up program: regular physical examinations and carcinoembryonic antigen test every 3 months and whole-body computed tomography (CT) every 6 months. A follow-up CT in February 2015 showed metachronous resectable liver metastasis. She...
was treated with seven courses of neoadjuvant chemotherapy with CapeOX (1,000 mg/m² capecitabine and 130 mg/m² oxaliplatin) plus bevacizumab (7.5 mg/kg). Segmental liver resection was performed in December 2015. Because CT in June 2016 showed metachronous resectable lung metastasis, partial resection of the right lung was performed in August 2016. After the operation, she was treated with four courses of adjuvant chemotherapy with CapeOX. In February 2018, carcinoembryonic antigen levels were found to be elevated at 8.5 ng/ml. In June 2018, a CT showed a cardiac tumour approximately 20 mm in size (Figure 1A and B) and multiple unilateral pulmonary tumours (Figure 1C and D). Furthermore, 18F-fluorodeoxyglucose positron emission tomography revealed significant accumulation in both cardiac and pulmonary tumours (Figure 1E). With regard to the cardiac tumour, magnetic resonance imaging showed an irregular 20-mm mass that was isointense on T1-weighted images, slightly more intense than the intact myocardium on T2-weighted images (Figure 1F and G), and characterised by a delayed enhancement. The patient underwent cardiac catheterisation with biopsy of the right atrial mass, which did not show any evidence of tumour cells. The cardiac catheterisation also revealed no intracardiac tumour or cardiac dysfunction. In July 2018, a limited excision biopsy was performed by minimally invasive cardiac surgery. A hard tumour of approximately 3 cm was detected at the apical part of the right ventricle during surgery and incisional biopsy of the tumour was performed. Microscopic pathological examination of the biopsy tissue confirmed metastatic adenocarcinoma, the histological features of which were similar to those of primary adenocarcinoma of the sigmoid colon. The tumour was deemed not suitable for resection and systemic chemotherapy was considered because multiple lung metastases coexisted. As the patient was 75 years old with an Eastern Cooperative Oncology Group performance status of 1, capecitabine and bevacizumab were administered. There was no grade 3-4 adverse event; therefore, the chemotherapy regimen was continued as scheduled with no dose reductions or discontinuation until June 2020 to ensure long-lasting stable disease (Figure 2). The clinical course since primary sigmoidectomy is shown in Figure 3. Written informed consent for patient information and images to be published was provided by the patient.

Discussion

We present a case of cardiac metastasis from CRC 5 years following primary tumour and hepatectomy/pulmonary resection for liver/pulmonary metastasis. The patient’s disease could be controlled for a prolonged duration by chemotherapy with capecitabine plus bevacizumab. There is no standardized approach or treatment for managing patients with cardiac metastases from CRC and the prognosis for patients with the metastatic cardiac tumours is unknown. Concerning the treatment of cardiac metastases from any malignancy, several reports emphasise the role of surgery based on significant improvements in survival times.
Murphy et al. performed operations on 19 patients with cardiac metastases and reported an operative survival of 68.4%, with a significant improvement in the quality of life and prolonged life expectancy (the average survival was 3.2 years for five patients) (6), which has confirmed by other reports (7, 8). Surgery may be indicated for palliation, when symptoms of haemodynamic compromise secondary to intra-cavitary tumour growth outweigh the risk of operative death, allowing more time for treatment with chemotherapy or radiation and increasing life expectancy (7). However, the potential survival benefit from cardiac surgery may be counterbalanced by perioperative morbidity and mortality. Therefore, indications for surgery in patients with metastatic cardiac tumours must be carefully considered, particularly for asymptomatic elderly patients or those with other metastatic lesions. Currently, little evidence is available regarding the efficacy of chemotherapy against cardiac metastasis from CRC; however, recently, the efficacy of combination therapy using cytotoxic drugs and molecular targeted agents such as anti-EGFR antibodies against cardiac metastasis from wild-type RAS CRC was reported (9). In the case of our patient, surgical resection of the cardiac metastasis was considered dangerous and unwarranted because of the presence of progressive lung metastasis. Furthermore, because the patient was aged ≥75 years, had a poor Eastern Cooperative Oncology Group performance status, and was considered unable to tolerate a doublet regimen, chemotherapy with capecitabine plus bevacizumab was introduced as first-line chemotherapy, as is typical for frail patients who are unsuitable candidates for intensive chemotherapy, according to the Japanese guidelines for unresectable advanced CRC (10).

Several concerns have risen about chemotherapy for elderly CRC patients owing to age-related comorbidities and functional status (11). Targeted agents, such as bevacizumab have been widely used for the treatment of metastatic CRC combined with chemotherapy (12). Bevacizumab, which has several side-effects, needs careful consideration when used for the treatment of elderly patients. The PRODIGE 20 study which evaluated chemotherapy associated with bevacizumab in patients aged 75 years or older demonstrated that bevacizumab in combination with both 5-fluourouracil monotherapy or doublet chemotherapy is well-tolerated and efficient in selected elderly patients (13). Longer tumour control is observed with chemotherapy plus bevacizumab than with chemotherapy only. Furthermore, normal independent activity, a positive daily living score, and no previous cardiovascular disease may predict good efficacy and safety.

Figure 2. Changes in metastatic lesions evaluated by computed tomography (CT) during capecitabine plus bevacizumab chemotherapy. The metastatic lesions remained approximately the same size. (A-C) CT findings of cardiac ventricular metastasis, (D-F) CT findings of one of the left lung metastases. (A, D) Baseline CT findings at the start of chemotherapy. (B, E) CT findings at 9 months after starting chemotherapy. (C, F) CT findings at 17 months after starting chemotherapy.
of both bevacizumab and chemotherapy in elderly patients with metastatic CRC (14). Because this case met the above points, bevacizumab combination regimen is considered promising in this case. Additionally, a phase III trial comparing capecitabine alone or combined with bevacizumab for elderly patients (AVEX trial) demonstrated that the combination of bevacizumab and capecitabine is an effective and well-tolerated regimen for elderly patients with metastatic CRC (15). Progression-free survival was significantly longer in the capecitabine plus bevacizumab group than in the capecitabine alone group [median=9.1 months (95% CI=7.3-11.4) vs. 5.1 months (95% CI=4.2-6.3); HR=0.53 (95% CI=0.41-0.69); p<0.0001]. However, as a demerit to choose a capecitabine plus bevacizumab regimen as first-line chemotherapy, there is a possibility that the following effective drugs may not be used up. These drugs include irinotecan, which has never been administered before in the diagnosis of myocardial metastasis, and anti-EGFR drugs which may exert effect in RAS wild-type CRC. However, it should be noted that several studies have demonstrated that doublet chemotherapy has a limited effect on progression-free survival and does not prolong overall survival compared to fluoropyrimidine alone in elderly patients (16, 17).

The right atrium and ventricle of the heart remain the most common sites of metastasis in the heart in most cases suggestive of haematogenous spread (18). Previously, a higher frequency of right atrial metastases than of right ventricular metastases from CRC was reported (19). We speculate that micrometastatic lesions that enter the heart through the systemic blood first reach the atrium, where the atrial blood flow is slower than the ventricular blood flow. Therefore, cancer cells have the potential to easily engraft in the atrial endocardium and myocardium. We found only 12 cases of well-documented metastatic CRC that involved the right ventricle of the heart. Table I shows 13 reports including the present case (3, 6, 9, 19-21). The median age at presentation in these reports was 71 years (range=55-77 years) with a slight prevalence in female patients (seven patients, 53.8%). Approximately half of the primary lesions were of the colic and rectal origins. Of the six cases in which tumour differentiation was described, there were four cases of moderately differentiated adenocarcinoma and one case of well differentiated adenocarcinoma and mucinous adenocarcinoma. Eight of the 13 cases were symptomatic, with symptoms such as dyspnoea and palpitation owing to congestive heart failure resulting from right ventricular outflow tract obstruction and valvular disorder. Solitary cardiac ventricular metastasis from CRC in the absence of lung and liver metastases is extremely rare (3). In this review, there were six cases with metastases other than cardiac metastasis at the time of the diagnosis of cardiac metastasis. Except for two cases whose treatment strategy is unknown, resection of cardiac metastasis and metastases other than cardiac metastasis was performed in one case. However, the outcome was death within 30 days after surgery, whereas chemotherapy was performed in three cases.
### Table I. Clinical features of cardiac right ventricular metastasis from colorectal cancer reported in English literature.

| Gender | Age | Primary tumor location | Primary tumor differentiation | Tumor stage | Symptoms | Diagnostic images | Definite diagnosis | Synchronous or metachronous | Other distant metastasis | Tumor size (cm) | Treatment of cardiac metastasis | Outcome | Author | Year |
|--------|-----|------------------------|-------------------------------|-------------|----------|-------------------|-------------------|------------------------|-------------------------|----------------|---------------------------------|---------|--------|------|
| Male   | 75  | Colon                  | muc                           | Stage IV    | Chest pain| Echo/MRI          | Autopsy           | Synchronous            | NA                      | 6x6x3         | Resection                       | In-hospital death | Massachusetts General Hospital Case Record | 1992 |
| Male   | 47  | Rectum                 | Adenocarcinoma                | NA          | Dyspnea, palpitation | TTE/MRI          | Resection          | Metachronous           | Absence                | 10x6x3.5      | Resection→ Chemotherapy (5-FU/levamisole) | Cancer death after 8 months of surgery due to recurrence of cerebral metastasis | Parravicini, R. | 1993 |
| Female | 71  | Rectum                 | Adenocarcinoma                | Stage III   | Dyspnea, anorexia | TTE              | NA                | NA                    | NA                     | NA            | In-hospital death                | Testempassi | 1994 |
| Male   | 71  | Rectum                 | tub2                          | Dukes C     | Dyspnea, anorexia | TTE              | Biopsy            | Metachronous           | NA                     | NA            | None                            | Tie, Hui | 1999 |
| Female | 71  | Rectum                 | Adenocarcinoma                | Dukes B     | Dyspnea, anorexia | TTE/CT            | Resection          | Metachronous           | Absence                | 5x3.5         | Resection                        | Lui      | 2004 |
| Female | 69  | Colon                  | Adenocarcinoma                | Dukes C     | Dyspnea, anorexia | TTE              | TTE               | Synchronous           | Presence               | NA            | None                            | Onegilia | 2005 |
| Female | 75  | Rectum                 | Adenocarcinoma                | Dukes B     | Dyspnea, anorexia | CT/MRI            | Not done           | Metachronous           | Presence               | NA            | Chemotherapy (capecitabine)      | Gaya, M. A. | 2005 |
| Female | 70  | Colon                  | tub2                          | Dukes C pT4 | Dyspnea, anorexia | TTE/CT/MRI/CT    | Biopsy            | Metachronous           | Absence                | 3.3           | None Chemotherapy (FOLFIRI) | Moreno-Vega | Patel, M. | 2006 |
| Female | 76  | Colon                  | tub2                          | Dukes C pT4 | None            | MRI/PET-CT       | Biopsy            | Metachronous           | Absence                | 6.4x5x2.6    | FOLFOX-6                        | Pizzianella | 2012 |
| Female | 77  | Colon                  | tub1                          | Stage IV    | None            | CT/MRI            | Not done           | Synchronous           | Presence               | 5x3.2         | Chemotherapy (FOLFIRI +Pmab)   | Yoshiki T | 2017 |
| Female | 45  | Rectum                 | Adenocarcinoma                | Stage IV    | None            | PET-CT            | Not done           | Synchronous           | Presence               | 1x0.9        | NA Chemotherapy (Capecitabine +Bmab) | Sarthak T | Present case | 2020 |

- tub1: Well differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma; muc: mucinous adenocarcinoma.
and a relatively good prognosis was achieved. However, resection was performed in two of four cases diagnosed only with cardiac ventricular metastasis. The outcome was death within 30 days after surgery in one case, whereas chemotherapy was effectively performed in the other two cases. Therefore, the surgical resection of the right ventricle may not be recommended owing to a high surgical risk and chemotherapy may be better than resection, especially in cases with metastases to other organs.

Conclusion

We encountered a patient who had cardiac right ventricular metastasis with lung metastases from CRC that could be controlled by capecitabine plus bevacizumab chemotherapy for a long time. The review of cardiac right ventricular metastasis from CRC demonstrated that the surgical risk of an operation to remove the right ventricle is high and not recommended. These findings suggest that chemotherapy may be suitable for selected patients with asymptomatic metastatic cardiac tumours; although to date, there are no standardised approaches to treatment in patients with cardiac metastases from CRCs. Further studies are needed to delineate the best treatment course in this group of patients.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors’ Contributions

SH, MM, SI: Drafted the manuscript; SH, MM, SI, HN, KS, TN, TI: contributed to patient care; SH, MM: performed the literature search; HE: advised on the oncological outcome; SH, MM, SI, TI: participated in the critical revision of the manuscript. All Authors read and approved the final manuscript.

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