

Case Series

Approach of oligometastatic cancer with intent of cure- exploring the road to recovery: interim analysis

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ABSTRACT

Oligometastases is a disease concept that is a state of limited systemic metastatic tumors defined in most studies as 1-3 or 1-5 metastatic lesions for which local therapy could be curative. Oligometastatic cancer has been traditionally managed by systemic therapy. With the hypothesis that not only long-term disease control, but also cure can be achieved in at least in a proportion of such patients, we analysed whether aggressive multimodality approach could become a new standard of care in highly selected patients with oligometastatic cancer. It is a case series of potentially curable oligometastatic cancers in our Institution approached with cure directed ablative/surgical procedures. An interim analysis was done after completion of all modalities of treatment and the outcomes analysed were local control/cure and disease-free survival. 15 patients were treated with curative intent which included eleven breast cancer and one each of gastric, OG junction, oesophagus, and rectal cancer. Metastases were treated with surgery in seven patients. Four patients were treated with SBRT, and EBRT was used in three other patients to treat metastases. Three patients had complete resolution of metastasis after chemotherapy. Disease-free/progression-free survival were compared with real world data where metastatic disease was treated with non-curative intent. The DFS/PFS for breast, gastric/oesophageal, and rectal cancer were 18.4 verses 6-13.3 months, 10.5 verses 5.6 months, and 15 verses 9.6 months respectively. Approaching oligometastasis with an intent of cure has shown to achieve reasonable local control/cure in our study and improve the DFS/PFS on comparison with real world data.

Keywords: Oligometastasis, Oligometastases, Oligometastatic cancer, Oligometastatic breast cancer, Metastatic cancer

INTRODUCTION

Oligometastases is a disease concept that is defined by a state of limited systemic metastatic tumors for which local ablative therapy could be curative. A malignancy that has progressed to a limited number of hematogenous metastases, defined in most studies as 1-3 or 1-5 metastatic lesions is defined as oligometastatic cancer.

There is no biomarker for the identification of patients with true oligometastatic disease and the diagnosis is based solely on imaging findings.^{1,2} The intent of treatment for oligometastatic cancer can be (a) to cure oligometastases,

(b) to prolong survival as a part of multidisciplinary therapy, or (c) local control for palliative care. Oligometastatic cancer has been traditionally managed by systemic therapy.

Based on anecdotal evidence, few metastatic cancers can go for complete remission and may have survival advantage. For these cancers, there is no consistent evidence on how to continue treatment. It may be wait and watch for disease progression, metronomic chemotherapy, continuation of systemic therapy eternally, multimodal management including surgery, or enrolling in a clinical trial.

Metastatic cancer is polyclonal and what remains after systemic therapy are the resistant clones, which if amenable to local treatment, can be treated with curative intent to achieve survival advantage. This idea has resulted in change of treatment paradigm for cancers with limited metastasis (oligometastases), i. e.; if the primary cancer site (if still present) is controlled, or resected, and the metastatic sites are ablated (surgically or with radiation), a prolonged disease-free interval, and perhaps even cure, may be achieved.

With the hypothesis that not only long-term disease control, but also cure can be achieved in at least in a proportion of such patients, we analysed whether aggressive multimodality approach could become a new standard of care in highly selected patients with oligometastatic cancer.

CASE SERIES

A series of potentially curable oligometastatic cancer patients approached with cure directed ablative/surgical procedures in our institution were studied.

Inclusion criteria

Patients with following criteria were included- (a) any primary solid malignancy with limited metastatic disease defined by 1-5 metastasis; (b) synchronous or metachronous oligometastases; and (c) oligorecurrent/oligopersistent/oligoprogressive disease with a controlled primary.

Inclusion criteria according to metastatic site

(a) Bone- mechanically stable, no epidural disease; (b) lung- absence of extra thoracic metastasis, metastasis amenable to complete resection, patient can tolerate the procedure, no better treatment alternative; (c) liver-adequate FLR and amenable to resection, responsive tumour to chemotherapy; (d) brain- limited brain metastasis 1-5 amenable to SBRT; and (e) on regional node- limited number 1-5.

Exclusion criteria

Patients with following criteria were excluded- (a) primary tumour not controlled; (b) lung or liver metastasis not amenable to surgical resection; and (c) poor performance status- ECOG 2 and above.

Patients were evaluated by imaging before and after initial therapeutic modality (chemotherapy or surgery). Patients with partial or complete response were treated with curative intent and patients with progressive disease were excluded. An interim analysis was done after completion of all modalities of treatment and the outcomes analysed were local control/cure and disease-free survival. Fifteen patients were treated with curative intent which included eleven breast cancer and one each of gastric, rectal and OG junction cancer. Three patients presented with metachronous solitary oligorecurrence in lymph node, liver, and brain respectively. All others were synchronous disease treated with neoadjuvant chemotherapy except for one patient. Metastases were treated with surgery in seven patients (Contralateral axillary lymph node dissection-3, Lateral pelvic node dissection-1, cerebellar metastasectomy-1, adrenalectomy-1, and hemihepatectomy-1). Four patients were treated with SBRT, one each for spine, sternum, lung, and liver, and EBRT was used in two patients to treat spine and cerebellar metastasis respectively. Three patients had complete resolution of metastasis after chemotherapy.

Local control/cure and DFS/PFS

Overall, 10 out of 15 patients achieved local cure during the study period. Two patients required dual modality (SBRT and hemihepatectomy for liver metastasis, EBRT and metastasectomy for cerebellar metastasis) to achieve local control. Disease-free/progression-free survival were compared with real world data where metastatic disease was treated with non-curative intent.³⁻⁵ On comparison, the median DFS/PFS for Breast cancer was 18.4 versus 6-13.3 months, 10.5 verses 5.6 months for gastric/OGJ/esophageal cancer and, 13 verses 9.6 months for rectal cancer. The results are summarized in Table 1.

Table 1: Summary of all patients.

S. no.	Primary	Metastasis site and number	State/sub-state	Primary treatment modality	Surgery for primary	Curative treatment of metastasis	Adjuvant treatment	State of metastasis	DFI (months)
1	OGJ	Liver, 1	Metachronous OR	Multimodal treatment- surgery and adjuvant chemoradiation	Trans hiatal esophagectomy	SBRT followed by surgery- left hemi hepatectomy	Nil	Cured	8 m till date
2	Stomach	Lung, 2	Synchronous OM	Chemotherapy	Total Gastrectomy with D2 lymphadenectomy	SBRT	Chemotherapy	Cured	10 m till date

Continued.

S. no.	Primary	Metastasis site and number	State/sub-state	Primary treatment modality	Surgery for primary	Curative treatment of metastasis	Adjuvant treatment	State of metastasis	DFI (months)
3	Esophagus	Adrenal, 1	Synchronous OM	Chemo radiation	Esophagectomy	Adrenalectomy	Chemotherapy	Cured	12 m
4	Rectum	Lateral pelvic nodes, 2 external iliac nodes	Synchronous OM	Chemo radiation	Abdominoperineal resection	Lateral Pelvic node dissection	Chemotherapy	Cured	13 m till date
5	Breast	CAM, 1	Metachronous OR	Multimodal treatment-Surgery and adjuvant chemo, radiation	MRM	Axillary lymph node dissection	Chemotherapy	Bone metastasis in 16 months managed by RT	16 m
6	Breast	CAM, 2	Synchronous OM	Chemotherapy	MRM	Axillary lymph node dissection	Radiation	Cured	20 m till date
7	Breast	CAM, 1	Synchronous OM	Chemotherapy	MRM	Axillary lymph node dissection	Radiation	Cured	15 m till date
8	Breast	Lung, 3	Synchronous OM	Chemotherapy	MRM	Chemotherapy	Radiation	Bone metastasis in 14 months 9 managed by RT	14 m
9	Breast	Bone-spine, 2	Synchronous OM	Chemotherapy	MRM	SBRT	Hormonal therapy	Bone metastasis in 13 months managed by RT	13 m
10	Breast	Lung and bone-spine, 5	Synchronous OM	Chemotherapy	MRM	Chemotherapy and EBRT to spine	Radiation	Bone metastasis in 27 months managed by RT	27 m
11	Breast	Brain-cerebellum, 1	Metachronous OR	Multimodal treatment-surgery, adjuvant chemo and radiation	BCS	WBRT, systemic therapy followed by resection of brain secondary	Nil	Cured	12 m till date
12	Breast	Renal- 1	Synchronous OM	Chemotherapy	MRM	Chemotherapy	Radiation, systemic therapy for one year	Cured	36 m till date
13	Breast	Lung, 3	Synchronous OM	Chemotherapy	MRM	Chemotherapy	Radiation, hormone-al therapy	Cured	9 m till date
14	Breast	Bone-spine, 3	Synchronous OM	Chemotherapy	MRM	EBRT	Radiation	Bone metastasis in 15 months managed by RT	15 m

DISCUSSION

Theories of metastasis evolved from ‘Seed and soil theory’ by Paget in 1889 to ‘Systemic theory’ by Fisher according to whom small/clinically apparent tumors were an early manifestation of systemic disease and nodal involvement was not part of an orderly contiguous extension but rather a marker of distant metastases. According to this theory, local control alone would not impact survival. Later, Spectrum theory first described for breast cancer metastases in 1994 according to which disease at the time of presentation fell into a spectrum ranging from indolent disease to widely metastatic and the degree of clonal evolution determines the ability of the tumor to metastasize.

The spectrum theory was refined just one year later to describe the limited metastasis of any solid tumor and the term ‘oligometastasis’ was coined by Hellman and Weichselbaum in 1995 based on a consideration of the multistep nature of cancer progression. Oligometastatic state was described as an ‘intermediate between purely localized lesions and those widely metastatic’.⁶⁻⁹ European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) published the consensus recommendations for characteristics and classification of the spectrum of oligometastasis, which is being prospectively evaluated by the Oligo care study.^{1,11}

Since the purpose of local treatment for oligometastases is cure, the primary outcome to be analysed should be disease-free survival and not progression-free survival which is usually the outcome measure in clinical trials of metastatic cancers after first line of therapy.

Oligometastatic breast cancer

We treated eleven patients of oligometastatic breast cancer (OMBC). Three patients had lung metastasis and three had bone metastasis. Three patients who had contralateral axillary node metastasis (CAM) were treated by axillary node dissection (ALND). Renal and Brain metastasis were present in one patient each. All these patients are disease-free till date with median DFS of 18.4 months. According to Zhang et al the prognosis of CAM patients was similar to that of N3M0 patients and significantly better than that of patients with distant organ involvement and concluded that CAM should be treated as local recurrence with aggressive and curative rather than palliative strategies with ALND and radiotherapy.¹²

In literature, the evidence for treatment of OMBC is weak.^{13,14} According to M1 trial by Badwe et al in the overall study population (N=350), patients with metastatic breast cancer who were responding to anthracycline based chemotherapy were found to have no benefit of loco-regional therapy (LRT) in terms of overall-survival.¹⁵ However, the oligometastatic sub group analysis was not done in this study. A phase III study in the Netherlands is

assessing the role of high dose chemotherapy with carboplatin, thiotepa, and cyclophosphamide in OMBC.

According to SABR-COMET phase 2 trial, stereotactic ablative radiotherapy (SBRT) was associated with an improvement in overall survival, meeting the primary endpoint of this trial, but three (4.5%) of 66 patients in the SABR group had treatment-related death and concluded that phase 3 trials are needed to conclusively show an overall survival benefit, and to determine the maximum number of metastatic lesions wherein SABR provides a benefit.¹⁶ We used SBRT in two patients of OMBC and EBRT to brain in one patient. Multiple trials are evaluating the use of SABR and/or traditional surgery in addition to standard of care systemic therapy in the first line setting for newly diagnosed OMBC. The median PFS in MBC is 6-13.3 months according to real world data where metastatic disease is treated with non-curative intent. On comparison, our study population shows better median DFS/PFS of 18.4 months.

Oligometastatic esophageal/gastric/OG junction cancer

Analysis by Salati et al showed better median overall survival (31.3 months vs 10 months) in carefully selected oligometastatic gastric cancer (OGC) treated by perioperative chemotherapy and surgery.¹⁷ AIO/FLOT3 trial paved way for the ongoing RENAISSANCE/AIO-FLOT5 trial which will shed more light in treatment of OGC. We treated two patients of oligometastatic gastric/OGJ cancer and one patient with esophageal (mid thoracic) cancer with median DFS of 10.5 months until the study period which is better on comparison with DFS of 5.6 months in real world data of metastatic Esophageal/Gastric cancer treated by palliative therapies. Further follow up is necessary to compare the overall survival with available literature. Markar et al who performed hepatic resections in select Gastric cancer patients concluded that the data presented should not be a rationale to change current clinical practice but rather a stimulus to prospectively study the role of surgery in a selected group of patients who are currently treated with palliative chemotherapy. This is applicable for our study too.

Oligometastatic rectal cancer- lateral lymph node dissection

We treated one patient with non-regional lateral lymph node metastasis of carcinoma rectum with Lateral lymph node dissection (LLND) along with Abdominoperineal resection after neoadjuvant chemoradiation. According to Fujita et al TME with LLND had a lower local recurrence, especially in the lateral pelvis, compared to TME alone and overall survival and local recurrence free survival were better with TME-LLND.¹⁹ However, this study had its limitation due to less statistical power and preoperative chemoradiation was not taken into consideration. According to Kim et al the size of the lateral lymph node and responsiveness to preoperative CRT should be the

main factors for selecting appropriate patients to undergo a LLND.²⁰ Zhou et al described that patients with pathological LPNM still show an elevated overall recurrence rate and poor prognosis after TME+LPND and strict patient selection with intensive perioperative chemotherapy is crucial to ensure the efficacy of LPND.²¹ The median PFS of metastatic rectal cancer treated by palliative therapies in real world is 9.6 months. Our patient is currently disease free for 13 months.

Pulmonary metastasis

According to IRLM Database and PulMiCC trial, resectability of the disease, single or multiple metastasis and DFI >36 months were considered to predict survival after pulmonary metastasectomy.²² Patients with favourable risk in all 3 criteria could anticipate 50% survival at 5 years compared to <15% with unfavourable risk in all 3 criteria. We treated four patients with oligometastasis to lung. One patient was treated with SBRT and the rest were treated with systemic therapy alone and no local treatment was necessary.

Liver metastasis

According to CLOCC trial, 119 patients with unresectable colorectal liver metastases (n<10 and no extrahepatic disease) received systemic treatment alone or systemic treatment plus aggressive local treatment by radiofrequency ablation±resection.²³ Overall-survival was better in multimodality treatment arm. We treated one patient of OG junction cancer who developed metachronous Oligorecurrence in liver. SBRT was used initially after which tumour was controlled but not cured. We performed left hemi hepatectomy and the patient is disease free for 8 months.

Brain metastasis

The treatment options for limited brain metastasis are a combination of surgery, whole brain RT (WBRT) and Stereotactic radiosurgery (SRS). According to Andrews et al (RTOG 9508), treatment with combination of SRS and WBRT showed better survival than WBRT alone (median OS 4.9 m verses 6 m).²⁴ According to JCOG0504, salvage SRS was non-inferior to salvage WBRT after surgery in limited brain metastasis.^{1-4,25} Available evidence shows that combination therapy has better survival for oligometastasis to brain. We treated our patient with a combination of WBRT and salvage surgery. The patient is disease-free for 12 months till date.

Local cure/control

10 out of 15 patients achieved local cure during the study period. Two patients required dual local modality for oligometastasis to achieve cure. There were no major toxicities or adverse events due to the local therapy and thus it can be said that local treatment of metastasis is safe and does not affect the quality of life. The median PFS in

5 patients who progressed was 17 months which showed better outcome when compared to PFS while treatment with palliative intent.

Limitations

Oligometastasis may denote indolent disease not warranting potentially toxic treatment. Locally directed treatment might not alter the natural course of the disease and the treatment paradigms are also controversial due to limited data available. Systemic therapy alone or in addition to local treatment will have some effect on micrometastases and would obscure the significance of local treatment. To reveal the significance of local treatment on the outcome of cure, the treatment modality for clinical research on oligometastases should only be local ablation. In our study chemotherapy was used as the only modality to treat metastasis in three cases which does not justify the need of locally directed treatment. According to available literature, biopsy is not mandatory to prove metastasis and diagnosis by imaging alone would suffice. This might lead to erroneous diagnosis of oligometastasis which could have happened in three of our cases that showed complete resolution of metastatic sites after chemotherapy. Our study has limited patients with inhomogeneous data which warrants prospective randomized study to arrive at a definite conclusion.

CONCLUSION

Approaching oligometastasis with an intent of cure has shown to achieve reasonable local control/cure in the interim analysis of our study and improved DFS/PFS on comparison with real world data. With randomized trials ongoing and treatment paradigms still evolving, whether treatment with curative intent will alter the landscape of oligometastatic cancer management remains unanswered. Our study has steered in right direction towards answering this question and long term follow up would throw more light in this regard.

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