



Oligometastases: history and future vision of breast cancer

Yuzuru Niibe¹, Keiichi Jingu², Hiroshi Onishi³

¹Department of Primary Care and Medical Education, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan; ²Department of Radiation Oncology, Graduate School of Medicine, Tohoku University, Sendai, Japan; ³Department of Radiology, Graduate School of Medicine, Yamanashi University, Yamanashi, Japan

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Correspondence to: Yuzuru Niibe, MD, PhD. Department of Primary Care and Medical Education, Okayama University, MUSCAT CUBE 2F, Shikata Campus, 2-5-1, Shikata-cho, Kita-ku, Okayama, 700-8558, Japan. Email: jo-niibe@google.com.

Abstract: Oligometastases, oligo-recurrence, sync-oligometastases and metachronous oligometastases were proposed based on the spectrum theory. This review article, first, described the history of cancer theory. Second, we described the history of the concepts of oligometastases, oligo-recurrence and sync-oligometastases. Finally, we prospect future visions of breast cancer of oligometastases.

Keywords: Oligometastases; oligo-recurrence; sync-oligometastases; metachronous oligometastases; breast cancer

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History of cancer theory

Patients with any metastatic or recurrent cancers were considered incurable and were not expected to survive for a long-term. Samuel Hellman proposed a new theory in 1994 at the Karnofsky Memorial Lecture (1). This theory was termed the spectrum theory. Until this theory was proposed, the systemic disease theory was accepted worldwide which indicated that all patients with cancer had potential metastases even if they did not have metastatic or recurrent cancer. Before the systemic disease theory was proposed by Bernard Fisher in 1980, cancer was considered to follow the Halsted theory, which was proposed by William Stewart Halsted in 1894. The Halsted theory suggested that if left untreated, cancer consecutively spreads through regional lymph nodes and then by hematogenous dissemination to the other organs in the body.

For a long time, there have been many investigations and discussions on where the systemic disease theory or spectrum theory is more accurate. Nowadays, the spectrum theory is well accepted among leading cancer professionals. The premise of the spectrum theory lies between the Halsted and systemic disease theories. According to his

hypothesis, cancer is a spectrum of diseases than ranges from being a local disease to one metastasizes.

Indeed, some cancers are both local and systemic, which can be described as a “spectrum”. Hellman suggested these differences raise the “tumor burden” in this hypothesis. Because, breast cancer tends to remain a local disease, as far as it is a small tumor. More recently, the concepts of oligometastases (2), oligo-recurrence (3-5), and sync-oligometastases (4) have been reported.

History of the concepts of oligometastases, oligo-recurrence and sync-oligometastases

In 1995, Hellman and Weichselbaum proposed the concept of “oligometastases” (1). This concept was based on the spectrum theory and expands beyond small breast cancer. In an editorial published in the *Journal of Clinical Oncology*, they suggested that some patients with cancer having metastases could have long-term survival. This was the first description of oligometastases and related concepts. Around the same time, Niibe trained as a medical intern at the National Institute of Radiological Sciences Hospital in Japan. He observed the disappearance of para-aortic lymph node

metastases with uterine cervical cancer patient, following treatment with external radiation therapy (6). Furthermore, he reviewed the medical charts of patients the same stage of the disease and who were previously treated with external radiation therapy alone or combined with systemic chemotherapy and found that they had long-term survival or were even cured. This experience gave him highly interest of cancer patients with metastases or recurrences, and he began investigating oligometastases: however, at that time, he was not aware of this concept because there was no internet or PubMed when he trained as a medial intern. After his experience, he wrote the original articles about par-aortic lymph node metastases or recurrences in patients with uterine cervical cancer (7-9), and in 2006, he finally proposed the concept of “oligo-recurrence”. The differences between oligometastases and oligo-recurrence were previously described in detail with figures (3,4). Briefly described here, Niibe *et al.* defined the concept of oligo-recurrence as the state in which patients had a controlled primary cancerous lesion and 1–5 metastatic or recurrent cancerous lesions, and all active cancerous lesions could be treated with local therapies, such as surgery, radiation therapy, radiofrequency ablation, and others with or without systemic therapy. In 2012, Niibe and Chang defined sync-oligometastases as the state in which patients with cancer have active primary cancerous lesions and 1–5 metastatic or recurrent cancerous lesions, and all active cancerous lesions require local treatment, with or without systemic therapy. This classification had very important implications in the oligometastases field because the prognosis of these patients was different. Patients with oligo-recurrence have significantly superior outcomes to those with sync-oligometastatic patients (5,6,10,11). These studies included a nationwide survey of 1,378 oligometastases patients published in 2020 (5). Nowadays, oligometastases is a generous technical term including oligo-recurrence, sync-oligometastases, oligoprogression and others.

The important caution was reported here. The concept of “metachronous Oligometastases” was proposed firstly by Niibe and Chang (4).

Future visions of breast cancer

In 2019, one of the biggest news concerning of oligometastases, COMET-SABR randomized phase 2 reported the final outcomes (12,13). These outcomes suggested that the median overall survival of the control group (palliation therapy) was 28 months, which was

significantly inferior to the 41-month overall survival of patient in the SABR group (hazard ratio: 0.57, 95% confidence interval: 0.30–1.10, $P=0.090$) (12). The finding of this study phase 2 randomized trial was significant as they applied a two-sided α of 0.20 and a power of 80%. Of the patients in this randomized phase 2 trial, 18% had breast cancer. However, the inclusion criteria of this randomized phase 2 study were limited to oligo-recurrence. The appropriate description of this study’s technical terms of oligometastases should be revised to oligo-recurrence when citing appropriate articles (3,4,14-17). This means that our proposed concept of oligo-recurrence and retrospective studies of oligo-recurrence are relevant to this randomized phase 2 trial (5,14,15). Thus, we re-emphasize here that the appropriate technical terms use of oligo-recurrence should be the standardized according to scientific society rules (15,16).

A prospective study for oligo-recurrence from breast cancer was reported in 2019 (18). This prospective study indicated that patient with 1–3 bone-only oligo-recurrences achieved both a long-term local progression-free survival (LPFS) and distant progression-free survival (DPFS). The LPFS was 100% at 2 years. The 1- and 2-year DPFS were 80% (95% CI: 62–100%) and 65% (95% CI: 45–95%), respectively. Many retrospective studies suggested that bone-only oligo-recurrences achieved longer survival rates compared with visceral oligo-recurrence (19-22). Although retrospective study, Miyata *et al.* showed that 90% of patients with oligo-recurrence in lymph node, soft tissue, visceral organ and bone had an objective response to salvage mainly conventional radiotherapy and the 3-year local control rate was 93% in Japan (22). Further stereotactic body radiotherapy (SBRT) for oligo-recurrence in regional lymph node from breast cancer without past irradiation history must be performed more proactively. Because, Jingu *et al.*, Yamashita *et al.* and Niibe *et al.* reported excellent results of esophageal or uterine cervical cancer lymph node oligo-recurrence treated by radiation therapy (23-25) and many radiation oncologists also experienced excellent results of breast lymph node oligo-recurrence. Moreover, SBRT are expected better outcomes of conventional radiation therapy with local control, survival and toxicities (5,26).

Further studies exploring the new age of metastatic breast cancer and even other cancers should include phase 3 clinical trials. To better understand, the detailed mechanisms of oligometastases, oligo-recurrence and sync-oligometastases, including the abscopal effect should also

be required (27-29). In this view point of breast cancer oligometastases, there is ongoing research in this field: the NRG-BR002 is a randomized phase II/III trial assessing the role of SBRT or surgical ablation for oligometastatic breast cancer patients (30). The authors expect clinical trials should require focus on the appropriate combinations of local therapy and systemic therapy, including immunoradiotherapy and others.

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