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Resection of the primary tumor in stage IV breast cancer

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Abstract

Stage IV breast cancer refers to breast cancer that has already metastasized to distant regions when initially diagnosed. Treatment for stage IV is intended to "prolong survival and palliate symptoms". Resection of a primary tumor is considered to be "effective only at alleviating chest symptoms and providing local control" in spite of the advances of imaging examination and medication for breast cancer. Molecular target and endocrine drugs are very effective and useful to tailor-make a treatment strategy according to breast cancer subtypes. Positron emission tomography-computed tomography can detect and diagnose the very small metastases and recurrences which can potentially be cured even if they are distant metastases. Recently, many retrospective studies have reported the survival benefit of surgery for breast cancer patients with metastases and some clinical trials which confirm the surgical prognostic benefit for them have started to enrol patients. The goal of treatment has to be clearly identified: increase the patient's survival time, provide local control or perform histology to determine the cancer's properties. The best evidence is absolutely essential to treat patients who need surgery at the right time. We need to evaluate the treatment strategy, including primary resection for stage IV breast

cancer particularly, and find new evidence by prospective analysis.

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Key words: Breast cancer; Metastasis; Surgery; Survival; Stage IV; Clinical trial

Core tip: Resection of a primary tumor of stage IV breast cancer was considered to be "effective only at alleviating chest symptoms and providing local control" in spite of the advances of imaging examination and medication for breast cancer. Recently, many retrospective studies have reported the survival benefit of surgery for breast cancer patients with metastases and some clinical trials which confirm the surgical prognostic benefit for them have started to enrol patients. We need to evaluate the treatment strategy, including primary resection for stage IV breast cancer particularly, and find new evidence by prospective analysis.

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INTRODUCTION

Stage IV breast cancer refers to breast cancer that has already metastasized to distant regions when initially diagnosed. Even if such cancer were to be treated, complete cure would not be expected. Treatment is intended to "prolong survival and palliate symptoms". Medication has made advances and treatments that are anticipated to be efficacious are administered. This situation has changed little as new drugs are coming out every year. In an increasing number of patients, appropriate use of

those drugs allows long-term control of symptoms and a longer life with disease.

In addition, marked advances in diagnostic imaging equipment have been made. Over the past few years, the prevalence of positron emission tomography-computed tomography has led to the early diagnosis of extremely small metastases that were not previously noted^[1]. Stage IV breast cancer with these small metastases is referred to as “minimal stage IV disease^[2]” and patients with this more limited form are expected to have a better prognosis than patients with full-blown stage IV breast cancer. Although it has yet to be precisely defined, the concept of “oligometastasis” is being debated^[3]. According to this concept, metastases can potentially be cured, even if they are distant metastases, depending on their location and number.

Resection of a primary tumor was previously considered to be “effective only at alleviating chest symptoms and providing local control”, but some studies have reported that resection increases survival time^[4,5]. Breast-conserving surgery is a widely used form of surgery for breast cancer. Anesthesia has also made advances and is safe. At the current point in time, surgery for breast cancer is extremely simple, depending on tumor size, and minimally invasive. A longer survival time seldom results from drug administration but it can result from surgery. Surgery for stage IV breast cancer is an important topic that may substantially alter future treatment strategies.

SIGNIFICANCE OF RESECTION OF THE PRIMARY TUMOR IN STAGE IV BREAST CANCER: STUDIES REPORTING INCREASED SURVIVAL TIMES AND RELATED ISSUES

As mentioned earlier, a number of recent studies have reported that surgery for stage IV breast cancer affects a patient’s survival time. Many of these retrospective studies indicated that surgery prolonged survival time. Several systematic reviews have reported significant differences in survival time (HR of about 0.6)^[4,5]. A look at subgroups indicates that factors facilitating surgery include “complete excision of the primary tumor”, “metastasis only to bone and/or soft tissue”, “few metastases” and “being younger”^[6,7]. A study reported differences in the effectiveness of surgery for different subtypes of tumors^[8]. However, all of the findings cited were the result of retrospective analysis so they are presumed to be highly biased. “Patients who undergo surgery” are invariably “patients in good enough condition to undergo surgery” while “patients who do not undergo surgery” are possibly “patients who are unable to undergo surgery because of their worsening condition”. In addition, medication has not been studied in detail and patients who undergo surgery are likely to include a number of patients whose condition could have been satisfactorily controlled with medication. The timing of surgery is also unclear. There

is no clear answer as to whether surgery should be done during initial treatment or whether it should be a final option that is used after medication proves inefficacious.

WHY DOES RESECTION OF ONLY THE PRIMARY TUMOR HELP WHEN CANCER CELLS HAVE SPREAD THROUGHOUT THE BODY?

According to the seed and soil theory by Paget^[9], the distant metastasis is not local disease. Cancer cells have already spread to whole body circulation. So, local therapies do not affect overall survival, whereas there are several theories on the basic rationale for resection of the primary tumor increasing the survival time for patients with stage IV breast cancer. The first is a “reduction in total tumor volume”. Circulating tumor cells (CTCs) are a major indicator of tumor volume. A reduction in CTCs is reported to be correlated with prognosis^[10]. Resection of the primary tumor reduces the tumor volume and thus reactivates autoimmunity and increases the efficacy of medication^[11]. A study prospectively demonstrated that resection of the primary tumor is useful when kidney cancer is in stage IV (this is the only other solid tumor besides breast cancer for which this holds true)^[12]. According to the study, resection of the primary tumor is a theoretical basis for the effectiveness of surgery.

Another theory as to why resection of the primary tumor increases the survival time concerns the particular action of the primary tumor. “Cancer stem cells” that are prevalent in the primary tumor are resistant to medication^[13]. In addition, the concept of “cell seeding” indicates that cells released into the blood by the primary tumor return to the primary tumor, so the primary tumor activates those cancer cells^[14]. Both of these mechanisms are based on results of basic experiments and no studies have described results from actual patients. If, however, they are true, then they are sure to be key to devising cancer treatment strategies in the future. These mechanisms should be verified in the future.

LOCAL CONTROL

As mentioned at the very beginning, resection of the primary tumor has been useful in alleviating chest symptoms, such as bleeding and ulceration as well as pain due to invasion of the chest wall. However, no studies or prospective trials have determined whether or not earlier surgery is useful to achieve local control. At the current time, there are absolutely no data corroborating the contention that “earlier surgery is useful since it improves local control, even if it does not increase survival time”. When local control alone was envisioned, radiation therapy was considered in addition to surgery. Although sample sizes are small, studies have described an improvement in the prognosis for the primary tumor in stage IV breast cancer as a result of radiation therapy (like the improvement in

Table 1 Ongoing randomized trials testing the worth of local therapy for an intact primary in women with stage IV breast cancer xvii

Country	Trial number	Accrual period	n	Initial therapy	Radiotherapy	Primary endpoint
India	NCT00193778	2005-12	350	Adriamycin-cytoxan	If indicated	Time to progression
Turkey	NCT00557986	2008-12	281	Surgery	For breast conservation	Survival
United States and Canada	NCT01242800	2011-16	368	Appropriate systemic therapy	Per standards for stage I -III	Survival
Netherlands	NCT01392586	2011-16	516	Surgery	For positive margins or palliation	2-yr survival
Austria	NCT01015625	2010-19	254	Surgery	Per standards for stage I -III	Survival
Japan	JCOG 1017	2011-16	410	Appropriate systemic therapy	No	Survival

JCOG: Japan Clinical Oncology Group; NCT number: A unique identification code given to each clinical study registered on ClinicalTrials.gov.

prognosis as a result of surgery)^[15]. In addition, a study has reported a satisfactory prognosis for asymptomatic rather than symptomatic patients, regardless of whether treatment was administered and regardless of the type of treatment^[16]. Results suggest that local control itself may act beneficially on prognosis, irrespective of whether treatment is classified as surgery, radiation, *etc.*

TRIALS CURRENTLY UNDERWAY TO DETERMINE THE USEFULNESS OF RESECTION OF THE PRIMARY TUMOR IN STAGE IV BREAST CANCER

As noted previously, there are absolutely no prospective data at the current time to corroborate the usefulness of resection of the primary tumor in stage IV breast cancer in terms of increasing survival time or improving local control. At the current time, there is no evidence actively in favor of such a resection. That said, many results of retrospective studies continue to be discussed in various fora. In the absence of robust evidence, this meta-analysis provides an evidence base for primary resection in the setting of stage IV breast cancer for appropriately selected patients^[17]. Resection of the primary tumor could greatly affect breast cancer care so this clinical question needs to be answered in prospective trials. Given this potential, 6 groups are currently enrolling patients^[18-20] (Table 1). The first reports of two prospective studies were indicated in the San Antonio Breast Cancer Symposium 2013^[21,22]. Both studies did not demonstrate a significant survival benefit of primary surgery. From the Indian trial, the distant disease free survival in the patients with surgery was significantly worse than that of the patients without surgery. One of the reasons was the insufficient systemic chemotherapy after surgery. They did not continue systemic chemotherapy after randomization and appropriate systemic therapies according to breast cancer subtypes were not selected in these protocols. So, the median survival time was shorter than that of retrospective European and American data. In particular, they did not use molecular target therapy for patients with human epidermal growth factor receptor type 2 positive breast cancer. Moreover, the diagnosis of metastasis was uncertain. They only used bone scintigraphy to diagnose a solitary bone metastasis. The Breast Cancer Study Group of

the Japan Clinical Oncology Group (1017) and Eastern Clinical Oncology Group (2108) began enrolling patients for a phase 3 trial in June 2011^[23]. Patients receive current standard systemic therapy before and after randomization and the latest imaging examination before treatment in these trials. A trial by the current authors is determining the significance of early resection of the primary tumor in stage IV breast cancer when that tumor can be controlled by medication. Items being assessed include the total survival time as well as the significance of local control; the results of the trial are sure to provide clinically significant evidence.

CONCLUSION

At the current point in time, one cannot say whether or not resection of the primary tumor provides a clear benefit in the management of stage IV breast cancer. Basic studies have revealed the biology of breast cancer in detail and the role of surgery is changing as treatment is better tailored to the individual in accordance with the individual's biology. The goal of treatment has to be clearly identified: increase the patient's survival time, provide local control or perform histology to determine the cancer's properties. Without a doubt, the best evidence is absolutely essential to treat patients who need surgery at the right time. Announcement of the results of clinical trials that are currently underway and examination of those results in detail are the first steps to obtain that evidence. However, obtaining results takes time and other strategies to treat breast cancer are constantly changing. In addition, the drugs used and patient attributes differ completely in different countries. An effective strategy to treat stage IV breast cancer must be devised in accordance with medication in light of the patient's symptoms while remaining mindful of the significance of surgery.

REFERENCES

- 1 **Ohsumi S**, Inoue T, Kiyoto S, Hara F, Takahashi M, Takabatake D, Takashima S, Aogi K, Takashima S. Detection of isolated ipsilateral regional lymph node recurrences by F18-fluorodeoxyglucose positron emission tomography-CT in follow-up of postoperative breast cancer patients. *Breast Cancer Res Treat* 2011; **130**: 267-272 [PMID: 21590272 DOI: 10.1007/s10549-011-1561-8]
- 2 **Niikura N**, Costelloe CM, Madewell JE, Hayashi N, Yu TK,

- Liu J, Palla SL, Tokuda Y, Theriault RL, Hortobagyi GN, Ueno NT. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. *Oncologist* 2011; **16**: 1111-1119 [PMID: 21765193 DOI: 10.1634/theoncologist.2011-0089]
- 3 **Pagani O**, Senkus E, Wood W, Colleoni M, Cufer T, Kyriakides S, Costa A, Winer EP, Cardoso F. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? *J Natl Cancer Inst* 2010; **102**: 456-463 [PMID: 20220104 DOI: 10.1093/jnci/djq029]
 - 4 **Petrelli F**, Barni S. Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. *Med Oncol* 2012; **29**: 3282-3290 [PMID: 22843291 DOI: 10.1007/s12032-012-0310-0]
 - 5 **Ruiterkamp J**, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF. Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. *Breast Cancer Res Treat* 2010; **120**: 9-16 [PMID: 20012891 DOI: 10.1007/s10549-009-0670-0]
 - 6 **Shien T**, Kinoshita T, Shimizu C, Hojo T, Taira N, Doihara H, Akashi-Tanaka S. Primary tumor resection improves the survival of younger patients with metastatic breast cancer. *Oncol Rep* 2009; **21**: 827-832 [PMID: 19212646]
 - 7 **Rapiti E**, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, Chappuis PO, Bouchardy C. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006; **24**: 2743-2749 [PMID: 16702580 DOI: 10.1200/JCO.2005.04.2226]
 - 8 **Neuman HB**, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer* 2010; **116**: 1226-1233 [PMID: 20101736 DOI: 10.1002/cncr.24873]
 - 9 **Paget S**. The distribution of secondary growths in cancer of the breast. *Lancet* 1889; **133**: 571-573 [DOI: 10.1016/S0140-6736(00)49915-0]
 - 10 **Budd GT**, Cristofanilli M, Ellis MJ, Stopeck A, Borden E, Miller MC, Matera J, Repollet M, Doyle GV, Terstappen LW, Hayes DF. Circulating tumor cells versus imaging-predicting overall survival in metastatic breast cancer. *Clin Cancer Res* 2006; **12**: 6403-6409 [PMID: 17085652 DOI: 10.1158/1078-0432.CCR-05-1769]
 - 11 **Danna EA**, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. *Cancer Res* 2004; **64**: 2205-2211 [PMID: 15026364 DOI: 10.1158/0008-5472.CAN-03-2646]
 - 12 **Flanigan RC**, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR, Munshi N, Crawford ED. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; **345**: 1655-1659 [PMID: 11759643 DOI: 10.1056/NEJMoa003013]
 - 13 **Kakarala M**, Wicha MS. Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy. *J Clin Oncol* 2008; **26**: 2813-2820 [PMID: 18539959 DOI: 10.1200/JCO.2008.16.3931]
 - 14 **Kim MY**, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, Massagué J. Tumor self-seeding by circulating cancer cells. *Cell* 2009; **139**: 1315-1326 [PMID: 20064377 DOI: 10.1016/j.cell.2009.11.025]
 - 15 **Lang JE**, Tereffe W, Mitchell MP, Rao R, Feng L, Meric-Bernstam F, Bedrosian I, Kuerer HM, Hunt KK, Hortobagyi GN, Babiera GV. Primary tumor extirpation in breast cancer patients who present with stage IV disease is associated with improved survival. *Ann Surg Oncol* 2013; **20**: 1893-1899 [PMID: 23306905 DOI: 10.1245/s10434-012-2844-y]
 - 16 **Hazard HW**, Gorla SR, Scholtens D, Kiel K, Gradishar WJ, Khan SA. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. *Cancer* 2008; **113**: 2011-2019 [PMID: 18780312 DOI: 10.1002/cncr.23870]
 - 17 **Khan SA**. Surgery for the intact primary and stage IV breast cancer...lacking "robust evidence". *Ann Surg Oncol* 2013; **20**: 2803-2805 [PMID: 23649932 DOI: 10.1245/s10434-013-3002-x]
 - 18 **Perez CB**, Khan SA. Local therapy for the primary breast tumor in women with metastatic disease. *Clin Adv Hematol Oncol* 2011; **9**: 112-119 [PMID: 22173605]
 - 19 **Soran A**, Ozbas S, Kelsey SF, Gulluoglu BM. Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. *Breast J* 2009; **15**: 399-403 [PMID: 19496782 DOI: 10.1111/j.1524-4741.2009.00744.x]
 - 20 **Ruiterkamp J**, Voogd AC, Tjan-Heijnen VC, Bosscha K, van der Linden YM, Rutgers EJ, Boven E, van der Sangen MJ, Ernst MF. SUBMIT: Systemic therapy with or without up front surgery of the primary tumor in breast cancer patients with distant metastases at initial presentation. *BMC Surg* 2012; **12**: 5 [PMID: 22469291 DOI: 10.1186/1471-2482-12-5]
 - 21 **Badwe R**, Parmar V, Hawaldar R, Nair N, Kaushik R, Siddique S, Navale A, Budrukkar A, Mittra I, Gupta S. San Antonio Breast Cancer Symposium. Abstract S2-02. San Antonio, USA, 2013
 - 22 **Soran A**, Ozmen V, Ozbas S, Karanlik H, Muslumanoğlu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T, Uras C, Aksaz E, Soyder A, Ugurlu U, Col C, Cabioglu N, Bozkurt B, Dagoglu T, Uzunkoy A, Dulger M, Koksall N, Cengiz O, Gulluoglu B, Unal B, Atalay C, Yildirim E, Erdem E, Salimoğlu S, Sezer A, Koyuncu A, Gurleyik G, Alagol H, Ulufi N, Berberoglu U, Kennard E, Kelsey S, Lembersky B. San Antonio Breast Cancer Symposium. Abstract S2-03. San Antonio, US, 2013
 - 23 **Shien T**, Nakamura K, Shibata T, Kinoshita T, Aogi K, Fujisawa T, Masuda N, Inoue K, Fukuda H, Iwata H. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. *Jpn J Clin Oncol* 2012; **42**: 970-973 [PMID: 22833684 DOI: 10.1093/jjco/hys120]

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