Peer Review File

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Reviewer A

1-1 Very well written case report.
Clinical course timeline is extremely helpful.
Please consider alternate title to clarify that patient was treated 24 years ago.
1-2 Please add in line citations for references.

Reply 1-1:
Thank you for your kind comments. we have modified our title as advise.

Changes in the text: (see Page1, line 1-3)

A Patient with Stage IIIB Advanced Breast Cancer who is Still Alive 24 Years After Surgery: Case Report; Remarks to the Treatment Strategies

Reply 1-2:
Thank you for your valuable advice. Several papers have been changed and added, based on the opinions of other reviewers as advise.

Changes in the text:
(see Page19, line420 - Page21, line478)

Reviewer B

Comment 2-1
“Hortobagyi” is cited 7 times in the manuscript: all 7 instances are misquote. The manuscript erroneously interprets the Horotbagyi paper. In fact, except for radiotherapy, the case is almost a textbook application of the 1998’s Hortobagyi recommendation. Specifically for Locally Advanced and Inflammatory Breast Cancer, Hortobagyi

recommended “stage III or locally advanced breast cancer should be treated with pre operative chemotherapy or hormonal therapy, surgery, and radiotherapy”.
Misquoting should be removed.

Reply 2-1: Thank you very much for your precious suggestions.
A review of Horotbagyi's original article clearly stated that chemotherapy, endocrine therapy, radiation therapy, and surgery can be used in all cases of metastatic breast cancer, and that optimal palliation and prolongation of life are the main goals of treatment. It also states that it is important to use all available treatment modalities and does not recommend treatment limited to endocrine therapy. We are sure that many clinicians, including myself, have misinterpreted the treatment Horotbagyi algorithm, so I have corrected it.
We have modified our text as advise.
(Horotbagyi certainly noted “Chemotherapy, hormonal therapy, radiotherapy, and limited surgery are all used in the treatment of women with metastatic breast cancer, although the overwhelming majority of these women will die of their disease. Therefore, optimal palliation and prolongation of life are the main goals of treatment. It is important to use all available treatments to obtain maximal control of symptoms, prevent serious complications, and prolong life with minimal disruption of the woman’s lifestyle and quality of life.”)

Changes in the text:：

(see Page3,line52-53) by the conventional treatment policy that emphasizes quality of life without aiming for complete cure.

(see Page3, line 62-Page4, line72) Therefore, it is widely treated by a misinterpretation of the conventional Hortobagyi treatment algorithm, which emphasizes quality of life and delays the start of highly invasive treatments as much as possible (1). Hortobagyi noted that it is important to use all available treatments to obtain maximal control of symptoms, prevent serious complications, and prolong life with minimal disruption of the woman’s lifestyle and quality of life. In the case of recurrent breast cancer, if the only destination is to prolong life without using all of these available treatments, this inevitably indicates that complete cure is not possible, and the patients are left with a deep sense of hopelessness.

(see Page11, line240-243) In addition, chemotherapy had been performed in this case, but currently, endocrine therapy is now widely used as the first choice for HR+ recurrent breast cancer patients based on a misinterpretation of the Hortobagyi treatment algorithm, if there are no life-threatening visceral metastases.

(see Page11, line246-248)
the treatment strategy is more likely to delay the start of chemotherapy and emphasizes quality of life.

(see Page13,line280-284) We consider that it is important to decide whether to follow the conventional treatment bound by a misinterpretation of the Hortobagyi algorithm and avoid highly invasive chemotherapy to prolong life and maintain quality of lifewithout aiming for complete cure, or to adopt a treatment strategy that aims for complete cure from the beginning.

(see Page13, line286-288) Although extreme, it may be speculated that if the patient had continued the endocrine therapy alone bound by the conventional treatment policy that emphasizes quality of life without aiming for complete cure.

(see Page15, line 342-345) it may be possible to select the treatment aiming for complete cure instead of the conventional treatment strategies bound by a misinterpretation of the Hortobagyi algorithm for recurrent breast cancer.

Comment 2-2
« Cure » in advanced breast cancer" is not new. Should refer to Patricia Tai who reported on the statistical cure of various cancers, among which regional and distant breast cancer.

Reply 2-2:
Thank you for your valuable advice. As you pointed out, after reviewing Patricia Tai's paper, I understand that long-term follow-up is necessary to estimate the statistical cure rate. I will refer to her paper when I analyze and report on long-term survival cases in the future. we have modified our text as advise and add her article in citations for references.

Changes in the text：

(see Page 9, line 205-Page 10, line 209) However, Patricia Tai states that a certain threshold number of years is required for long-term survival of cancer, especially breast and thyroid cancer, which require longer follow-up than other cancers, and the definition of long-term survival for breast cancer may be different from that of other cancers. (6)

(see Page 19, line 432-434)6. Tai P, Yu E, Cserni G, et al. Minimum follow-up time required for the estimation of statistical cure of cancer patients: verification using data from 42 cancer sites in the SEER database. BMC Cancer. 2005;5:48.

Comment 2-3

Should discuss the limitation of the case report. There are two patterns of disease progression, local-regional, and distant. The patient's first 8 years was mostly regional, with normal CEA. Later when the patient recurred, CEA also increased, most likely in relation with the development of macro-metastases. In order to have an insight into the local or distant phenotypic manifestations, this case could have benefited from:

1) FDG PET

2) Circulating tumor cells / liquid biopsy monitoring.

Reply 2-3:

Thank you for your valuable advice. We agree with your opinion. Different from large clinical trials, case reports cannot provide an accurate basis in determining a treatment decision.

Therefore, we hope that this report will raise issues and encourage other clinicians and researchers to rethink their treatment strategies for recurrent and metastatic breast cancer.

We are certain that the long-term DFS in this case, as you mentioned, is due to adequate local control as the initial treatment. As for the late recurrence, it is likely that stem cells and other factors were involved, causing macro-metastases.

Today, with the availability of liquid biopsy, a recurrence could have been detected at an earlier stage. We also regret that we should have done more periodic PET-CT.

We have mentioned our thoughts based on your advice in our discussion as follows

Changes in the text：

(see Page 16 line 346- line352) This report is only one small case report and does not have the power to determine significant changes in the current treatment strategies for recurrent advanced breast cancer. However, we hope that medical professionals involved in the treatment of breast cancer around the world will consider all possibilities to improve the prognosis of current patients with recurrent or metastatic breast cancer, and that new treatment strategies will be obtained through maximum cooperation between basic medical researchers and clinical physicians.

Comment 2-4

Overall, the manuscript should highlight what makes this case report unique. There is no surgeon alive who has enough experience to practice radical Halsted mastectomy. Typically, modern patients with pectoralis involvement will be left as-is without any attempt to further surgery. These patients can have prolonged survival, but typically within 1-2 years develop local recurrences. Their local recurrences are so terribly intractable that oncologist don't even bother to look under the wound dressings. The manuscript's case 8-years freedom from local recurrence is probably attributable to the surgery, and not to any systemic manipulation. The surgeon who performed the pectoralis resection should be congratulated. Manuscript should raise the question whether mastectomy should be universally denigrated. Regarding the patient's global health, the manuscript should report whether the patient was physically impaired or not.

Reply 2-4

Thank you for your valuable comments based on your extensive experience. We strongly agree that the importance of local control is currently underestimated in advanced breast cancer.

Recently, I fear that too much attention has been paid recently to less invasive surgical methods, which may lead to a misunderstanding of the nature of treatment.

When I was a resident, all cases of advanced breast cancer were treated with practice radical Halsted mastectomy. In some cases, the clavicle was removed for thorough lymph node dissection, and the clavicle was repaired after dissection. Although such surgery is now considered excessively invasive, I personally feel that the OS and DFS of patients who actually underwent such surgery was good. In addition, such surgery does not cause significant muscle weakness or nerve damage, and the patient in this case had no numbness or muscle weakness that interfered with his daily life.

As you say, there are probably very few surgeons who can perform a complete Halstead procedure today. I have been performed Halstead surgery, modified radical mastectomy

(Patey method), Kodama method and the current pectoral muscle-sparing surgery, and I do not think that enlargement surgery is entirely meaningless in view of the prognosis based on my experience to date. We have made the following additions to the discussion to include our experiences.

Changes in the text:：

(see Page 10, line 215-228) We would like to mention one thing here about the significance of initial surgery. Currently, in the treatment of advanced breast cancer, the importance of surgery, the classic method of local control, may be often neglected in contrast to the rapidly developing systematic therapy using with rapid advent of agents possessing novel mechanisms. In this case, however, complete resection of the tumor, including the pectoralis major muscle, as the initial treatment provided sufficient local control, which may have enabled long-term disease control. An initial surgical treatment is undoubtedly important in a treatment strategy of complete cure. A total mastectomy, including the surrounding tissue, is certainly an important first step toward a complete cure. This case rases an critical question of whether mastectomy, including the pectoralis major muscle and other surrounding tissues, should be universally denied for the treatment of advanced breast cancer.

(see Page 8, line 165-166)

Also, there is no evidence of muscle weakness or neuropathy due to pectoralis major muscle resection at present.

Comment 2-5

Minor: Line 137 “At November 2021, approximately 18 years after the first recurrence”: erroneous calculation? According to the report the first recurrence occurred in 2006 (line 103).

Reply 2-5　Thank you for your valuable suggestions.

We have corrected the numbers as you indicated.

Changes in the text:：

(see Page7, line161) At November 2021, approximately 15 years after the first recurrence

Reviewer C

This manuscript provides an interesting perspective on the sequence of treatment in the HR+ breast cancer. This case report of a patient with stage IIIB breast cancer treated upfront with the more aggressive treatments illuminates an interesting standpoint on the conventional Hortobagyi treatment algorithm. I do want to mention thought that the sequencing of the treatments including upfront endocrine therapy vs. chemotherapy has been evaluated in the decade long clinical trials.
This manuscript illuminates and interesting discussion point in the future clinical strategies.
I do recommend this manuscript for the publications with minor revisions which would include the fixing the grammar and streamlining abstract.
Line 325: CDK4/6 inhibitors appear in the middle of the page

Reply 3　Thank you for your kind comments. We also looked up the sequencing of the treatments including upfront endocrine therapy vs. chemotherapy and confirmed that there are reports as you indicated. Thank you for pointing this out. we have added another article in citations for references.
The words “CDK4/6 inhibitor” have been deleted.
We have also reduced the number of words in the abstract to 306.Changes Changes in the text：

(see Page19 line 418)　“CDK4/6 inhibitor” have been deleted.

(see Page20 line 442-443)

9. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev 2003:CD002747.