Editorial

Treatment redirection from cure to palliation, then cure again?—a cautious, but urgent matter

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In general, advanced lung cancers that have been either diagnosed initially as systemic metastatic disease or recurrent after curative-intended surgical resection are regarded as palliative conditions with low probabilities of long-term survival. However, post-recurrence survival (PRS) for patients has gained recent attention, because encouraging new treatments, such as target-directed therapies and immune checkpoint inhibitors, have provided better long-term survival and quality of life in selected patients with recurrent or metastatic diseases (1-3). There have been several studies of PRS after curative resection in patients with early stage lung cancer. A series of studies from Taiwan were examples, which claimed that both complete surgical resection for local recurrent disease and systemic treatment for distant failure significantly prolong PRS (4,5). However, in these investigations, the cumulative probability of PRS was less than 10%, regardless of the recurrence pattern, and thus the radical local control has generally not been recommended, except for very uncommon cases.

In contrast to the findings presented above, a Japanese group recently investigated whether survival of sufficiently long duration (more than 5 years after recurrence) depends on the situation, with or without cancer progression (6). They reported that the outcome from the initial surgical treatment was quite similar to others, with a median recurrence-free survival (RFS) and PRS time of 24 (range, 0–153) months and 9 (range, 0–138) months, respectively. However, they had seen the patients continuously even after the recurrence and, managed enthusiastically. The clinicopathological features of patients who survived for 5years after the initial recurrence (n=51 out of 635 recurrent lung cancer patients) were compared with those who did not survive for 5 years (n=584 out of 635 recurrent lung cancer patients), and this analysis revealed that the female sex, adenocarcinoma histology, absence of distant metastases, and longer RFS significantly associate with prolonged PRS.

Then, authors analyzed the subsequent outcomes of all 5-year survivors, regardless of the recurrence status, according to their clinical status at postoperative 5 years.

The 5-year survivors were first classified into two groups based on the presence of progressive disease: a cancer-controlled group, which included patients without progressive disease or further treatment (n=19 out of 51 5-year survivors after recurrence), and a cancer-bearing group, which included patients with progressive disease or under treatment (n=32 out of 51 5-year survivors after recurrence). Outcome were, as hypothesized, dramatically better in the cancer-controlled group than in the cancer-bearing group [8-year (96 months) PRS: 94% *vs.* 31%, P=0.003]. If we carefully change 'the cancer-controlled group' to 'recurrent patients without cancer', and 'cancer-bearing group' to 'recurrent patients with cancer', we can easily follow the findings from this study, which

suggests that radical local therapy with a curative intent may significantly improve the survival of the patients with recurrence.

This is not necessarily a new observation, because survival outcomes of patients with second primary lung cancer after effective local control consistently show promise. However, the authors suggest that the candidate for the local control be extended to systemically metastasized lesions if completely removed.

This is very delicate and maybe too hasty suggestion. Some may argue that the original recurrent patterns of the cancer control group were good to be controlled or the patients were strong enough to endure more radical procedures. In contrast, in cancer bearing group, the patients had initially multiple systemic metastasis including bones, and poorer performance, which limited their endurance of comparative management. In this study, it might be true. In the cancer-controlled group, 17 of the 19 (89%) patients initially received radical local therapy including surgery and radiotherapy. In contrast, only 18 of the 32 (56%) patients in the cancer-bearing group initially could have received radical local therapy.

Then, based on this study, 'with the hope of better survival, should we afford more aggressive mode of management to the recurrent patients?'

The answer would be 'No, not yet!'

Although there has been increased attention to PRS, standard treatment strategies have yet to be established and should not be set without sound evidence, for examples, large-scale databases and/or prospective studies.

This may be very difficult because of the extreme diversity of the clinical courses, treatment methods, recurrence patterns and so on, even the performance status. However, because there has been rapid increase in recurrent patients after surgery due to earlier detection and curative-intended surgeries, the establishment of standard treatment strategy should not be disregarded or deferred too long. Moreover, because of earlier detection of recurrence by closer follow-up and advanced image techniques, more recurrent patients are functionally too good to be considered as candidates for palliative care.

To speak frankly, cure as treatment direction sounds quite attractive and natural to health care providers. Therefore, it has taken very difficult and long time to redirect treatment goals from cure to palliation in patients and families with very limited quantities and qualities of life. One of the most common reasons to lose the appropriate time for treatment redirection has been that clinicians and patients focus only on the cure.

Every oncologist, regardless of specialty such as surgical, radiation, or medical, should keep in mind Potter's warning, who said, "*Physicians often assume that patients and families want everything done, even if it will provide little or no benefit. Although sometimes this is true, it should not be assumed without clarification of the patient's and family's expectations.*" However, "*evidence-based medical decisions can be claimed for no more than fifteen to twenty percent of clinical situations. Even though guidelines for recognizing terminal prognoses are of proven value, there is a persistent resistance among clinicians to use them.*" (7).

In consideration of this argument, what then would be the prudent attitude to deal with this issue of increasing importance? Although not entirely encompassing and ideal, followings should be considered.

First, the best supportive care under palliative purposes should nevertheless be mainstay in the management until sufficient evidence is collected (8) and assessed at a multi-disciplinary discussion table. Physicians, especially cancer surgeons, generally do not have enough knowledge about palliative care and portray negative attitudes toward its embracement. There has been more local control of recurrent tumors when surgeons themselves follow up with patients after operation, and therefore every decision about radical local control should be made through sufficient discussion of various management approaches.

Secondly, more attention and concern should be placed upon the potential hazards of local control to patients. Complications related to the procedures and quality of life after treatment should be systematically assessed and closely monitored for sufficient lengths of time. Even minor events, such as poor appetite or intermittent aching pain at the chest, might seriously affect quality of life and ultimately shorten life expectancy in patients who are elderly and/or with co-morbidities (9,10). The risk of mortality and morbidity by radical local therapy for recurrent lesions, by estimation, should not exceed those of surgery for the initial lung cancer.

Thirdly, we should begin by building reliable database systems for patients with recurrent lung cancer that are systematic but separate from that of patients initially diagnosed with metastatic cancers. In practice, this may be difficult due to extreme diversity of clinical courses, treatment methods, recurrence patterns, and other reasons such as performance status, however this should be the starting line for establishing a standard treatment strategy. The incorporated data should include preoperative status, performance studies, operative procedures, detailed

systematic node dissections, pathological findings (with subtypes), postoperative follow-up information, recurrence pattern and dynamics, and serial managements post recurrence. While any single group may not have had enough data to fulfil such requirements, ideally, with enough initiative to collect retrospective study information, we can acquire step-by-step guidelines and studies for respective clinical situations.

Fourthly, there should be additional diagnostic tools implemented to determine cancer status that go beyond image-based assessments, such as CT, MRI, or PET-CT, and ideally such methodologies would be developed based on biological characteristics of respective cancers. While we do not yet possess such methods, circulating tumor makers, such as circulating cell-free DNA (cfDNA) or circulating tumor cells, show promise. There may be differential patient outcomes based on the presence of circulating tumor markers (11-13). Or, patients with greater tumor mutation burdens by circulating biomarkers may have better or worse outcomes by radical local control with systemic immunotherapy.

Moreover, knowledge pertaining to how the host immune system performs against cancer would guide radical local control decisions. For example, the grade of cytotoxic T cell infiltrate in a newly taken biopsy of recurrent lesions (14), TCRs against specific neoantigens (15,16) or the presence of certain gut microbiomes (17) should be considered. Additional surrogate markers will aid the appropriate stratification and selection of patients.

In a conclusion, the appropriate approach in the management of patients with recurrent lung cancer should be discussed and studied more and urgently. Although some reports have shown promising results, they cannot be generalized to every patient. Openness and prudence should be maintained to avoid inadvertent harm to helpless patients, which can happen through hasty decisions. As old saying says, '*One swallow does not make a summer*'.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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