Editorial

Editorial on "Long-term survival outcome after postoperative recurrence of non-small cell lung cancer: who is 'cured' from postoperative recurrence?"

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There is little knowledge or comprehensive research on the outcome of long-term surviving patients after postoperative recurrence of non-small cell lung cancer (NSCLC) and initially curative surgery for the primary lung cancer. Although in many cancer entities 5-year survival after treatment of primary cancer may result in a cure, in lung cancer patients the risk of late recurrence and second primary lung cancer remains high. In the management of this entity, we normally add patients who develop recurrence to the group of patients with stage IV disease. Postoperative recurrent NSCLC can be seen frequently in a range of 19.3% to 75% (1-5), and most of these patients will die of their disease. The median time from surgical resection of the primary lung cancer to loco-regional recurrent disease is 13.9 and 12.5 months for distant recurrence (6), and the median reported post-recurrent survival time for this very heterogeneous subset of patients ranges from 8.1 to 20.7 months (1,7-9). In general, recurrence is considered local or loco-regional when recurrent disease is within the ipsilateral hemithorax, mediastinum, or supraclavicular lymph nodes. All other sites of recurrence are considered distant metastases.

Differential diagnosis of lung cancer recurrence and metachronous primary lung cancer remains controversial because the differential criteria are not firmly established (10,11). Only in patients where histopathology and molecular analysis of the primary lung cancer and the returning tumor are available is it possible to differentiate between a second primary and a recurrent cancer—which in clinical practice is not always possible.

There is no standard definition for the state of recurrence in patients with NSCLC.

In the September 2017 issue of the *European Journal of Cardio-Thoracic Surgery*, Sekihara and coworkers (12) provide an elegant analysis of 635 (28%) patients who were identified as having developed recurrence disease out of 2,273 consecutive patients after complete R0 resection of NSCLC at the National Cancer Center Hospital East, Japan, between January 1993 and December 2006. In this study patients surviving after treatment of recurrent disease were classified in two groups: patients whose cancer was controlled with either no detectable lesions or lesions that remained stable without treatment and patients who were still carrying a progressive burden of disease (12). The reported evidence of late returning lung cancer, after 5 or more years, is between 9% and 10.6% with a local recurrence rate of 4.6% and 6% (13,14). Whether recurrent disease has been detected early or late after primary surgery for lung cancer seems to be of importance for long-term survival and underlines the importance of a systematic early postoperative surveillance strategy. In surgically resected patients the risk of distant metastases is greater than the

risk of local and regional recurrence, with local recurrence rates between 20.5% and 28.8%, distant recurrence rates of 67.8% to 79.5%, and mixed local and distant recurrence rates of 3.4–6.4%, respectively (1,14,15). The independently associated prognosticators for recurrence of NSCLC after complete surgical resection of the primary tumor include SUV_{max} greater than 5, more advanced pathologic stage, and preoperative radiation. Most likely, preoperative radiation will have been used to treat more aggressive tumors (16), which of course influences the risk of cancer recurrence. In another study of NSCLC, more advanced pathologic stage, advanced age, pneumonectomy, sublobar resection, lymphatic and blood vessel invasion, and visceral pleural invasion were independently associated with a greater risk of local and distant recurrence (1). Additionally, lymphovascular invasion of the primary tumor was found to be an independent predictor of distant (16), overall (17), and locoregional recurrence (18).

Considering that the vast majority of patients have inoperable recurrent disease on re-presentation, we should reconsider whether long-term follow-up should include the regular use of CT and positron emission tomography-CT (PET-CT) in all patients or whether it should simply be done when symptoms occur. However, an accurate understanding of the patterns of failure after surgery is essential to guide appropriate adjuvant therapy. Thus, when recurrence is suspected, PET-CT should be applied, because it can allow molecular imaging and further patient selection.

Recent data of post-recurrence survival by Sekihara *et al.* have detailed predictors, showing the best survival rates for patients who received radical local therapy for their recurrences, which led to a state of cancer-control or cancer-free status (12). Favourable post-recurrent survival has been seen to associate with female gender, adenocarcinoma histology, a long disease-free interval between treatment of the primary lung cancer and the onset of cancer recurrence, and locoregionally confined recurrent disease (12).

Local treatment options for patients with systemic therapy and a state of oligo-recurrence or oligo-progression of a single metastasis while all others remain stable (oligo-progression) may translate into long-term survival (19). The introduction of targeted and new immunotherapies for recurrent lung cancer interpreted as stage IV disease have changed our patient management significantly. In patients with treatment for recurrent disease, targeted therapies may lead to long-term cancer-bearing survivors with a more than 5-year post-recurrent survival (12). This may be one step in the attempt to transform systemic cancer into a chronic disease which can be controlled with modern systemic therapies and in some cases with local therapy. Further emerging molecular data may improve patient identification beyond clinical factors to guide patient selection with post-surgical recurrent disease for a more aggressive treatment approach.

Nevertheless, according to a study by Sekihara *et al.* only 13% of post-recurrent patients survive more than 5 years, most of them in a cancer-bearing state (63%) (12). Patients who survive 5 years with a cancer controlled status (37%) and no signs or symptoms of cancer can be considered survivors who may be possibly cured of disease. In this small subgroup, even 8 years overall survival rates of 94% were reported (12).

In the future, we must discuss whether patients with recurrent NSCLC must be treated differently than those with clinical stage IV disease. Besides stage IV disease and the newly defined entities of oligometastases, recurrence after curative treatment of lung cancer has to be considered as a further state of disease with its own laws and behavior. In this context, we have to approach the open question: what is the best surveillance strategy for patients who have been treated for lung cancer recurrence and how long should it be applied? Our main goal should be directed at prolonging post-recurrence survival in patients with a good performance status and stable or no detectable disease. In the management of patients with suspicion of recurrence, ^{18}F-FDG PET/CT is significant and can rule out recurrence in 24.2% of patients (20). However, further evidence is still necessary to develop more personalized programs of surveillance in this highly selected patient group.

In summary, for patients with new and limited sites of disease, local recurrence-directed therapies with radiotherapy or surgery should be considered.

In this way, patients can be rendered free of macroscopically visible disease and the use of chemotherapy can be appropriately relegated to the goal of eradicating microscopic disease (21). Therefore, the treatment and prognosis of postoperative recurrence must differ in some aspects from those used for clinical stage IV NSCLC. In the attempt to prolong post-recurrence survival, all available treatment modalities, i.e., surgery, chemotherapy, and radiotherapy, applied individually or in combination, should be discussed in a multidisciplinary tumor board (8).

Finally, the limitations of the data used for in the published literature should be mentioned. These include

the retrospective nature of the published data—especially in the context of significant developments in modern imaging techniques (PET-CT)—the lack of systematic follow-up methods, and changes in both surgical and adjuvant treatment regimens over time.

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Footnote

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

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