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Treatment options for isolated locoregional recurrences of nonsmall cell lung cancer after surgery: yes, radiation therapy too!

To the Editor:

In a recent article, SUBOTIC *et al.* [1] summarised the importance of salvage surgery in treating local or loco-regional, post-surgical recurrences in patients with, mostly, early stage nonsmall cell lung cancer (NSCLC). While the feasibility of such an approach is indisputable, we believe that the readership of the *European Respiratory Journal* should be made aware of another treatment option already successfully used in this setting, namely, radiation therapy. This is especially important in patients with less favourable features, where secondary surgery may not be an option. Other authors have already shown that such patients comprise the majority of the patient population, with salvage surgery being possible in just 4% of cases. Taking this into consideration may give the treating physicians a better perspective and also enable a more meaningful discussion on optimising both the standard clinical and investigational approaches in any future endeavours in this setting.

Traditionally, loco/regional recurrence may be divided into chest wall/pleural, parenchymal, bronchial stump, mediastinal lymph node recurrence or a combination of any of these. Radiation therapy has already been successfully used previously in all of the aforementioned settings and its value in the treatment of

recurrent NSCLC is recognised and well described in the literature. Earlier studies [2], as well as newer reports on radiation therapy alone or combined with chemotherapy [3, 4], showed it to be both effective and safe, with low toxicity in this setting. These studies also provided a framework that enabled an important observation, namely that the location of recurrence may ultimately influence the treatment outcome; recurrences located in the bronchial stump were associated with a much better prognosis than recurrences located in the chest wall/pleura or mediastinal lymph nodes.

Focusing on isolated bronchial stump recurrences, JEREMIC and BAMBERG [3] documented excellent median survival of ~28.5 months and a 5-year survival >30%. Furthermore, in a subset of patients with T2N0 bronchial stump recurrences in the study of JEREMIC *et al.* [5], high-dose radiation therapy (≥ 60 Gy) achieved excellent survival (5-year overall survival 57%), not inferior to survival obtainable with surgery alone or combined with other therapeutic modalities in newly diagnosed NSCLC of the same stage [6, 7].

Even when considering cases with a “more extensive” bronchial or tracheal component of the disease (with no nodal or other components present) [8] a median survival time of 19 months and 3-year survival of 12.5% can be achieved. Contrary to that, when bronchial stump recurrence was accompanied with nodal recurrences, the outcome became dismal [5, 9].

However, newer studies showed better survival in patients with a mediastinal recurrence [10]. CAI *et al.* [7] compared the survival of post-resection recurrent *versus* newly diagnosed NSCLC patients treated with radiation therapy combined with radio- or chemotherapy in 661 patients, of which 54 had post-resection recurrent and 607 had newly diagnosed NSCLC. The median survival time and 5-year overall survival rates (19.8 months and 14.8% *versus* 12.2 months and 11.0% for the two treatment groups, respectively ($p=0.037$)) clearly favoured the recurrent cancers, but for stages I–III there was no statistically significant difference observed in the 5-year overall survival ($p=0.297$) or progression-free survival ($p=0.935$) between recurrent and newly diagnosed patients.

Finally, a recently published study from TAKENAKA *et al.* [4] showed that combined radio-/chemotherapy is a promising option for patients with post-surgical recurrence. In this single institution study, 35 patients (24 nodal, six bone and five lung) were treated with a curative intent and a median dose of 60 Gy combined with a platinum-based chemotherapy regimen. This concept resulted in a median post-recurrence survival of 31 (range 5–127) months with survival being better in patients with nodal recurrence.

In conclusion, the available evidence shows that patients with post-resection recurrent NSCLC can achieve excellent results when treated with radiation therapy alone or with radio-chemotherapy. It reiterates that patients with post-resection recurrent cancers should be treated as aggressively as those with newly diagnosed disease.

Furthermore, the significant perioperative mortality together with the limited patient collective, where a surgical approach is applicable, proof that radiation therapy alone or combined with chemotherapy as an attractive alternative must be considered.

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Radiation therapy remains an excellent treatment option for selected patients with post-resection recurrent NSCLC <http://ow.ly/YZ6yc>

Nikola Cihoric¹, Alexandros Tsikkinis¹, Nenad Filipovic² and Branislav Jeremic^{2,3}

¹Dept of Radiation Oncology, Bern University Hospital and University of Bern, Bern, Switzerland. ²BioIRC Center for Biomedical Research, Kragujevac, Serbia. ³Institute of Lung Diseases, Sremska Kamenica, Serbia.

Correspondence: Nikola Cihoric, Dept of Radiation Oncology, Inselspital Universitätsspital Bern, Freiburgstrasse 10, 3010 Bern, Switzerland. E-mail: nikola.cihoric@gmail.com

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Radiation therapy for post-operative recurrence: yes, but only for limited indications

From the authors:

We read the correspondence of Cihoric and colleagues related to our editorial with great interest. Radiation therapy, either alone or in combination with chemotherapy, is a widely accepted treatment modality for post-operative lung cancer relapse. The focus of our editorial was to increase the awareness of possible repeat intervention in this quite limited patient group with generally poor prognosis [1]. Although the overall message of this correspondence is not debatable, the statement that “the available evidence shows that patients with post-resection recurrent nonsmall cell lung cancer (NSCLC) can achieve excellent results when treated with radiation therapy alone, or with radio-chemotherapy” is somewhat misleading as we have several concerns related to the evidence supporting the above statement.

The analysis cited under reference 5 in the correspondence included patients treated at the radiation therapy department in the period 1982–1993 [2]. In this series, both preoperative and post-recurrence work-up was unclear as computed tomography scans only became mandatory after 1988. Selection criteria for initial surgery are unknown, as well as criteria to reject patients with relapse from repeat surgery. With such an inconsistent or unclear preoperative work-up, well before the era of positron emission tomography and mediastinoscopy, it does not seem appropriate to compare survival of patients with isolated bronchial stump recurrences with survival of patients with surgery alone (or combined with other therapeutic modalities) in newly diagnosed T2N0 NSCLC.

Furthermore, comparison of survival of patients with post-surgery recurrence *versus* newly diagnosed NSCLC patients treated with radiation therapy or combined radio-/chemotherapy is not very helpful in optimising a therapeutic approach for cases of post-operative relapse [3].

We agree that combined radio-/chemotherapy is a promising option for patients with a post-surgical recurrence, as in the single-centre study of TAKENAKA *et al.* [4], but studies comparing repeat surgery with radio-/chemotherapy or with radiation therapy alone are missing. Similarly, the results of the systematic review cited under the reference 3 in the correspondence from Cihoric and colleagues, with median survival times of ~28.5 months and a 5-year survival in excess of 30%, emerged from considerations of treatment modalities with radiation therapy alone [5].

In addition, there are some general concerns when comparing surgery with the newly introduced stereotactic radiation therapy: specific pathological diagnosis is not obtained in every case; lymph node evaluation is less rigorously performed; and evaluation of treatment is quite challenging after stereotactic radiation therapy due to the inflammatory response and fibrosis that invariably occur [6, 7]. After complete surgical resection this is more straightforward as there is no remaining disease. For this reason direct comparison between surgery and radiation therapy is not possible [7].

In conclusion, radiation treatment remains an alternative treatment option for post-surgical lung cancer relapse, especially for those patients that are functionally inoperable or technically unresectable. Further evidence is certainly needed to develop more general recommendations for treatment of recurrent disease.