

Stereotactic ablative radiotherapy for early stage non-small cell lung cancer: a word of caution

Gonzalo Varela, María Teresa Gómez-Hernández

Thoracic Surgery Service, Salamanca University Hospital and Salamanca's Bio-sanitary Institute (IBSAL), Salamanca, Spain

Correspondence to: Dr. Gonzalo Varela. Cirugía Torácica, Hospital Universitario, Paseo de San Vicente 58, 37007 Salamanca, Spain. Email: gvs@usal.es.

Abstract: Recently published data from pooled randomised trials conclude that stereotactic ablative radiotherapy (SABR) can be considered the treatment of choice in operable lung cancer patients fit for lobectomy. This conclusion comes for comparable 3-year survival and much lower risk of early severe morbidity and mortality. In this editorial comment we discuss the validity of the conclusions due to the prematurity of the survival analysis and to the poor accuracy of patients' staging leading to higher rates of regional relapse in the SABR arm. Besides, therapy-related mortality and morbidity in the pooled cohort is much higher than the internationally accepted standards maybe because surgery was not performed according to the best approaches and procedures currently available. The effectiveness of SABR as the sole therapy for resectable lung cancer is still awaiting for sound evidences. It could be adopted for individual cases only in two situations: (I) the patient does not accept surgical treatment; and (II) in cases where the risk of surgical related mortality is considered to exceed the probability of long-term survival after lung resection. For this, a multidisciplinary team (MDT) assessment, including surgeons and oncologists, is mandatory.

Keywords: Lung cancer; pulmonary resection; radiotherapy

Submitted Sep 03, 2015. Accepted for publication Sep 14, 2015.

doi: 10.3978/j.issn.2218-6751.2015.10.10

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2015.10.10>

In a recently published issue at the *Lancet Oncology*, the authors reported a pooled analysis of two randomised trials [STARS (NCT02357992) and ROSEL (NCT00687986)] comparing stereotactic ablative radiotherapy (SABR) and lobectomy for operable stage I non-small cell lung cancer (NSCLC) (1).

Although the second was closed prematurely due to slow accrual, the authors conclude that SABR can be considered a treatment option in operable patients fit for lobectomy and that future randomised trials including more cases are warranted. The first conclusion comes from the statistically significant advantage on 3-year overall survival in the SABR-treated pooled cohort (although the difference was significant in the STARS trial alone) and from a higher rate of severe treatment-related complications in the surgical arm. In fact, overall surgical mortality was 4% (1/27) and grade 3-4 treatment-related adverse events were 44% (12/27). These data were compared to 0% mortality and 10% (3/31) grade 3 adverse events in the SABR arm.

Any new therapeutic option offering comparable outcomes at a lower risk for the patient has to be praised and disseminated as much as possible. The only condition for doing so is that therapeutic recommendations have to be supported on strong evidence.

Is survival really comparable?

In the aforementioned publication (1), it is to note that in the SABR series, almost 13% of the cases (4/31) suffered from regional lymph node relapse while in the surgical arm, the rate was only 3.7% (1/27) at 3 years. Higher rate of loco-regional relapse has been also reported by Versteegen *et al.* (2), comparing SABR *vs.* video-assisted thoracic surgery (VATS); these authors also found comparable 3-year survival in surgical and SABRT series.

Higher rates of loco-regional relapse in patients treated with radiotherapy can be justified in part by the superiority of intraoperative surgical staging if compared

to clinical staging by FDG-PET image or invasive procedures. Although the authors underline that clinical staging was accomplished in both trials by image (CT and PET scan) and endobronchial fine-needle aspiration or mediastinoscopy when indicated, it is well known that the accuracy of surgical staging is higher (3-5) allowing for adjuvant therapies in surgically staged N1 or N2 cases. Thus, waiting for 5-year survival data in both trials before recommending non-surgical therapy in early stage NSCLC would be advisable. Furthermore, in the ROSEL study, eight (26%) tumours in the SABR group had unknown histology and one patient without histological diagnosis in the surgical group underwent resection and were found to have benign disease. So the proportion of patients who had NSCLC or benign disease in the SABR group remains unclear. This lack of information could have contributed to an increased survival rate in the SABR group.

As more interim analysis on 3-year survival are reported, there is an increasing feeling that SABR or related techniques are equally effective than surgery for early lung cancer. In a publication from Ricardi *et al.* (6), reporting their results in a series of cases, it is stated that “The results of the present study support the routine use of SABR for stage I NSCLC in a daily practice environment”. Such a kind of statements are lacking enough evidence, especially if the new therapy is intended as a substitute of a historically proven effective treatment for early stage lung cancer.

Reported adverse effects of surgery are higher than the internationally accepted standards

High reported surgical mortality (4%) and grade 3-4 morbidity (44%) in the pooled cohort deserves some comments. According to the last report from the European Society of Thoracic Surgeons Database, the standard surgical mortality after lobectomy for lung cancer, in any pathological stage, in Europe is 2% (7), half the reported mortality in Chang's *et al.* paper (1). Due to the low number of cases in the pooled analysis, these differences are probably not statistically significant but they are clinically relevant especially because only stage I cases, where surgical mortality is highly infrequent, were included in both trials.

Also the high rate of major adverse events after surgical therapy has to be regarded with caution. Among the cases included in the SABR group, only three cases (10%) suffered treatment-related grade 3 adverse events: chest wall pain in three (10%), dyspnoea or cough in two (6%) and fatigue and rib fracture in one case (3%). No patient

experienced treatment-related grade 4 toxic effect. On the contrary, in the surgical group, 12 (44%) patients had grade 3-4 related adverse events. Again from the ESTS Database, the rate of major cardio-pulmonary complications after lobectomy, in any pathological stage, is 17.8% (7). Obviously, the accuracy in recording adverse events in a prospective clinical trial is non comparable to a multi-institutional database where participation is not mandatory. Nevertheless, the difference seems to be large enough as to be accepted without any criticism.

Standardising surgical procedures is much more difficult if compared to radiotherapy. In both trials surgical approach was either thoracotomy or VATS at surgeon's choice. Out of the 27 patients who received surgery, only five had VATS lobectomies, while 19 cases were approached through thoracotomy (in the rest of the cases the procedure was not completed). The term thoracotomy includes any open approach coming from posterolateral incision sectioning latissimus dorsi and serratus anterior muscles, to axillary mini-thoracotomy; that is, any approach were a rib spreader is used. All these approaches are quite different in terms of inflammatory response (8) and related complications. Lung resection for NSCLC is nowadays usually performed through a mini-invasive approach frequently video-assisted. This approach has been demonstrated to produce less short term and long term complications (9) and being equally effective in terms of survival (10,11). Thus, it seems to be logical, when designing a trial to compare the last available technique in radiotherapy to any surgical treatment, selecting also the least aggressive surgical technique, instead of obsolete approaches, to obtain conclusive results.

In the past we have shown that the majority of the risk of lobectomy depends not on patients' conditions but on the quality of the perioperative care (12). Unfortunately, both trials lack precise information on the type of perioperative care received by the patients. It has to be supposed that in both situations the best available care was offered to the patients but this doesn't guarantee the homogeneity of the pooled series with respect to the most relevant variable influencing immediate patients' outcome.

What does it mean “medically inoperable”?

In some of the recently published papers where SABR or any other modality of radiotherapy is offered as an alternative to lung resection, surgery was not considered because patients were: “medically inoperable” (6,13,14). Nevertheless, the specific reasons for inoperability are not

stated clearly. Obviously, any therapy shortening patient's survival is not indicated.

To our mind, the most accurate recommendations to evaluate patients' functional operability have been published in 2013 by Brunelli *et al.* (15). Shortly, these authors recommend:

- (I) Decision on lung cancer therapy has to be agreed by a multidisciplinary team (MDT);
- (II) Patient's age per se is not a contraindication for surgery;
- (III) Cardiologic consultation is needed after specific cardiac risk scoring for thoracic procedures is calculated;
- (IV) Estimation of postoperative FEV1 and DLCO is mandatory in all cases;
- (V) Exercise tests, starting by low technology ones, have to be indicated in cases with limited estimated postoperative FEV1 and/or DLCO (under 60% of theoretical values for age, sex and height).

Maybe the most important and simplest recommendation regarding therapy for lung cancer is that all therapeutically decisions have to be adopted after discussion in a MDT. MDT management has become the standard of care in some countries, after some advantages to both the patient and the clinicians have been demonstrated (16). In our practice, we noticed a slight decrease in lung resection related mortality after implementing internationally accepted guidelines and MDT agreement before indicating surgical therapy for lung cancer patients (17).

In summary, the effectiveness of SABR as the sole therapy for resectable lung cancer is still awaiting for sound evidences. It could be adopted for individual cases only in two situations: (I) the patient does not accept surgical treatment; and (II) in cases where the risk of surgical related mortality is considered to exceed the probability of long-term survival after lung resection. For this, a MDT assessment, including surgeons and oncologists, is mandatory.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Editorial Board Member Ying Liang (Department of

Medical Oncology, Sun Yat-sen University Cancer Center (SYSUCC), Guangzhou, China)

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630-7.
2. Versteegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. *Ann Oncol* 2013;24:1543-8.
3. D'Cunha J, Herndon JE 2nd, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. *Lung Cancer* 2005;48:241-6.
4. Shingyoji M, Nakajima T, Yoshino M, et al. Endobronchial ultrasonography for positron emission tomography and computed tomography-negative lymph node staging in non-small cell lung cancer. *Ann Thorac Surg* 2014;98:1762-7.
5. Whitson BA, Groth SS, Madaus MA. Surgical assessment and intraoperative management of mediastinal lymph nodes in non-small cell lung cancer. *Ann Thorac Surg* 2007;84:1059-65.
6. Ricardi U, Frezza G, Filippi AR, et al. Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: an Italian multicenter observational study. *Lung Cancer* 2014;84:248-53.
7. European Society of Thoracic Surgeons Database Committee. Database Annual Report 2015. Available online: http://www.ests.org/_userfiles/pages/files/ESTS%20201Silver_Book_FULL_PEF.pdf, accessed on Aug 30th, 2015.
8. Yim AP, Wan S, Lee TW, et al. VATS lobectomy reduces cytokine responses compared with conventional surgery. *Ann Thorac Surg* 2000;70:243-7.
9. Falcoz PE, Puyraveau M, Thomas PA, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg* 2016;49:602-9.
10. Higuchi M, Yaginuma H, Yonechi A, et al. Long-term

- outcomes after video-assisted thoracic surgery (VATS) lobectomy versus lobectomy via open thoracotomy for clinical stage IA non-small cell lung cancer. *J Cardiothorac Surg* 2014;9:88.
11. Yan TD, Black D, Bannon PG, et al. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol* 2009;27:2553-62.
 12. Novoa N, Ballesteros E, Jiménez MF, et al. Chest physiotherapy revisited: evaluation of its influence on the pulmonary morbidity after pulmonary resection. *Eur J Cardiothorac Surg* 2011;40:130-4.
 13. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010;28:928-35.
 14. Lanni TB Jr, Grills IS, Kestin LL, et al. Stereotactic radiotherapy reduces treatment cost while improving overall survival and local control over standard fractionated radiation therapy for medically inoperable non-small-cell lung cancer. *Am J Clin Oncol* 2011;34:494-8.
 15. Brunelli A, Kim AW, Berger KI, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e166S-90S.
 16. Powell HA, Baldwin DR. Multidisciplinary team management in thoracic oncology: more than just a concept? *Eur Respir J* 2014;43:1776-86.
 17. Novoa N, Jiménez MF, Aranda JL, et al. Effect of implementing the European guidelines for functional evaluation before lung resection on cardiorespiratory morbidity and 30-day mortality in lung cancer patients: a case-control study on a matched series of patients. *Eur J Cardiothorac Surg* 2014;45:e89-93; discussion e93.

Cite this article as: Varela G, Gómez-Hernández MT. Stereotactic ablative radiotherapy for early stage non-small cell lung cancer: a word of caution. *Transl Lung Cancer Res* 2016;5(1):102-105. doi: 10.3978/j.issn.2218-6751.2015.10.10