Editorial

Stereotactic ablative body radiation therapy or surgery for operable early non-small cell lung cancer patients: bound hand and foot to evidence

Antonin Levy[1,2,3], Olaf Mercier[2,4], Cécile Le Péchoux[1]

[1]Department of Radiation Oncology, Institut d'Oncologie Thoracique (IOT), Gustave Roussy, Université Paris-Saclay, Villejuif, France; [2]Univ Paris Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, France; [3]INSERM U1030, Molecular Radiotherapy, Gustave Roussy, Université Paris-Saclay, Villejuif, France; [4]Department of Thoracic and Vascular Surgery and Heart-Lung Transplantation, Institut d'Oncologie Thoracique (IOT), Marie-Lannelongue Hospital, Paris-Saclay University, Le Plessis Robinson, France

Correspondence to: Antonin Levy, MD. Department of Radiation Oncology, Institut d'Oncologie Thoracique (IOT), Gustave Roussy, Université Paris-Saclay, F-94805, Villejuif, France. Email: Antonin.LEVY@gustaveroussy.fr.

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Surgery is the standard treatment for operable early stage (stage I: T1–T2N0M0) non-small cell lung cancer (NSCLC) patients. Lobectomy, the surgical resection of a single lobe, is generally accepted as the standard procedure, since sublobar resection has not proved to provide equivalent results yet (1). Video-assisted thoracoscopic surgery (VATS) is becoming the gold standard surgical approach compared to open thoracotomy, as there is no difference in outcomes (2,3). Importantly, a systematic lymph node dissection should be performed in all cases to ensure complete resection. The 5-year overall survival (OS) is 47–51% in patients with clinical stage IA–IB, and 58–73% in surgically staged IA–IB patients, respectively (4). The incidence of local recurrence ranged from 7–23% in large surgical retrospective studies (5,6).

Within the recent years, stereotactic ablative body radiation therapy (SABR) [or stereotactic body radiotherapy (SBRT)] has become the standard of care in non-operable early stage NSCLC patients. SABR is an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions. Given that this technique demonstrated high local control rate (85–95%), and a low toxicity profile (7), SABR has been experimentally proposed to a limited number of operable patients with encouraging results (8-10).

Several retrospective studies (overviews, matched-pair analyses and meta-analysis based on the literature) have tried to compare surgery and SABR with conflicting results. This is not surprising given that non-comparable patients have been included. SABR patients were generally inoperable, with higher comorbidities scores (11-14). Death, in the SABR population, is mostly due to intercurrent causes, and OS may then not be considered as a valid comparison endpoint (15). It is also likely that SABR and surgical populations itself were heterogeneous. Surgical procedures differed in reported series (wedge resection, segmentectomy, lobectomy, VATS or open surgery). Several critical factors for local control in SABR patients (mainly the tumor volume and the dose of irradiation) have been highlighted and varied widely in different protocols (16). The definition of the local relapse (within the planned target volume (PTV) or within the lobe), the prescription criteria (at the isocenter or at an encompassed isodose), and procedures for diagnosing relapses are others parameters that largely differ in series, thereby making comparisons more difficult. Finally, the absence of accurate node sampling prior to treatment in SABR patients may lead to a clinical under-staging. Retrospectives series have yet

showed that occult node metastasis can occur in 5–10% of selected stage IA NSCLC (17).

As an example, the last recently published meta-analysis by Deng *et al.* meets the previously described criteria. Selected retrospective studies integrated non-comparable (SABR *vs.* surgery) patients with mixed populations. Inoperable SABR patients had poorer conditions (older, higher comorbidities scores, and poorer respiratory tests results) than surgical patients, leading to decreased OS. Surgical and SABR technical procedures varied broadly and/or were not reported (12,18,19). In conclusion, existing retrospective data, including meta-analysis on the literature, should be interpreted with extreme caution (11-14).

There is few (mainly two small non-randomized phase II) available, but promising, prospective data on SABR in operable patients. In the Japan Clinical Oncology Group (JCOG) study 0403, SABR (48 Gy in 4 fractions) was delivered in 65/169 (38%) operable patients with histologically or cytologically proven peripheral cT1N0M0 NSCLC. The 3-year OS, progression-free survival (PFS), local PFS, and event-free survival rates were 76.5%, 68.6%, 54.5%, and 51.4%, respectively. The most frequent failure was distant metastases in 21 (33%) cases, followed by 16 (25%) regional lymph node failures (20). In the preliminary results of the Radiation Therapy Oncology Group (RTOG) 0618 phase II trial including 26 evaluable patients, the total prescribed SABR dose was 54 Gy delivered in 3 fractions. The 2-year estimates of local failure (primary tumor plus involved lobe failure), regional failure, and distant failures rates were 19.2%, 11.7%, and 15.4%, respectively (21).

Three randomized trials have failed to compare SABR to surgery in operable patients due to poor accrual (ACOSOG Z4099, ROSEL and STARS trials). Data from prematurely terminated STARS and ROSEL studies were pooled but the analysis of the included 58 patients could at best be hypothesis generating (10). New comparative randomized studies are ongoing such as POSTILV (NCT01753414), SABRtooth (NCT02629458), STABLE-MATES (NCT02468024; two later studies including borderline operable patients), and the Veterans Affairs VALOR (NCT02984761, active but not yet recruiting). Only such prospective randomized studies, including quality of life and cost analyses, will really be able to conclude if SABR should be proposed in operable early-stage NSCLC patients.

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Footnote

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

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