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Robotic-assisted thoracoscopic surgery for clinically stage IIIA (c-N2) NSCLC – is it justified?

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Work-up as well as management of patients with non-small cell lung cancer (NSCLC) and clinically suspicious mediastinal lymph nodes (c-N2) should consider current guidelines (1), although the final implementation differs between several institutions and countries.

The authors have selected upfront surgery without prior invasive or non-invasive mediastinal staging and assessed the short-term outcome of robotic assisted surgery (RATS) in comparison to thoracotomy in a multicenter randomized controlled trial (2). No meaningful differences were found in most of the parameters, besides significant differences in intraoperative blood loss, drainage time, and postoperative pain (2).

The question, whether these short-term outcome parameters are relevant for the evaluation of treatment quality and efficacy of patients with locally advanced lung cancer, may lead to a controversial discussion, particularly in relation to the more relevant long-term outcome results. Patients and doctors most likely agree that overall- (OS) and disease-free survival (DFS) in a lung cancer operation is most important and side effects from surgery such as drainage and hospitalisation time are clearly less meaningful. OS and DFS after surgery for clinical stage III (N2) depends on two main factors, such as complete resection of the tumor, a so called R0-resection and definitive pathological mediastinal lymph node stage. The latter guides the need for adjuvant therapy including adjuvant chemotherapy, targeted treatment, immunotherapy, and radiotherapy. OS and DFS were not assessed in the reported trial but R0 and R1 resection were equal in both groups indicating that

radicality of surgery was comparable in both groups, and independent from the approach. This was found already in multiple studies before, which compared video-assisted thoracoscopic surgery (VATS) with thoracotomy in early stage lung cancer up to a tumor size of less than 3 cm (3,4). Furthermore, these studies showed that survival after resection was comparable for both approaches (5-10). In some studies, comprehensive reviews and meta-analyses, VATS was even comparing favorably to thoracotomy with survival advantage for VATS procedure.

Two published comparisons of long-term oncologic outcomes of robotic lobectomy for early-stage NSCLC versus VATS and open thoracotomy approach show that RATS lobectomy was associated with durable freedom of recurrence and long-term survival equivalent to those achieved with VATS and the traditional open thoracotomy approach. As presented by the Italian group of Veronesi *et al.*, RATS approach for locally advanced NSCLC with clinically evident or occult N2 is safe and feasible with 3- and 5-year OS at 61.2% and 49% respectively (11).

In term of radical R0-resection of early stage lung cancer with RATS compared with VATS, there were also no quality issues in the literature and comparison between minimally invasive (RATS and VATS) versus open lobectomy of locally advanced NSCLC achieved a similar R0 resection rate between the groups (12).

The second key issue of an oncologically correct lung cancer operation is the extent of hilar and mediastinal lymph node clearance. The number of lymph nodes and the number of lymph node stations resected represents figures

of lymph adenectomy completeness. The pathological result may lead to recommendations for or against adjuvant therapy. In addition, in this regard, both study arms showed the same number of investigated lymph nodes. Since all patients had upfront surgery without induction chemo- or chemoradiation and the lymph node removal extent was limited to resectable ones in this trial, the result is not a surprise. It has been shown also in many series comparing VATS with thoracotomies (4,8,13-16) that lymph node resection can be done in at least equal quality using the minimal invasive approach. RATS compared to VATS came to similar results (17-19). Furthermore, Merritt and colleagues show, that mean numbers of total lymph nodes and N2 lymph nodes were significantly higher in the robotic lobectomy group ($P < 0.0001$) (20).

Many centers would assess enlarged mediastinal lymph nodes by EBUS or mediastinoscopy and in case of histologically proven mediastinal disease would initiate neoadjuvant chemo- or chemoradiation prior to resection. Surgery thereafter is occasionally more difficult because the dissection planes may be fused and lymph nodes may become adherent to vessels (such as v. cava, pulmonary vessels) or the trachea. It would be interesting to compare the open technique with RATS after neo-adjuvant therapy when downstaging occurred and the dissecting planes fibrous and lymph nodes stick to vessels, airways, and esophagus. The procedure is then more of a challenge and patients undergoing RATS lobectomy after induction chemotherapy with or without radiation therapy may be at greater risk for recurrent laryngeal nerve injury, tracheal/bronchial injury, and pulmonary embolism (21). Furthermore, as presented by Veronesi and colleagues, on robotic resection of stage III lung cancer patients after induction chemotherapy, required in 15% conversion and 12% patients developed grade III or IV postoperative complications (11).

Intraoperative blood loss was significantly different when comparing the two surgical approaches. The question comes up, if a difference of 80 mL is clinically meaningful or not. Blood loss has a negative influence on OS after lung cancer operations (22). However, only when the amount of blood loss is larger than 80 mL a relevant impact on the immune system may occur. On the other hand, a blood loss of only 80 mL in the RATS group may be an indicator, that RATS allows very precise and most atraumatic surgery, which is often stated by RATS surgeons. The reason includes facts such as the excellent 3D view, instruments which allow a precise dissecting technique, and possible also the fact, that

a surgeon needs to avoid even the smallest bleeding in order to have a good view and control of the operation.

Drainage time and the amount of drainage fluid differed statistically between the groups but with a relatively minor clinical meaning. The same can be said for pain management. Early postoperative pain was clearly less in RATS treated patients, which is an advantage. But, the pain in the thoracotomy group seems to be manageable looking at the difference in the visual analog scale.

What can we finally conclude from this randomized trial comparing RATS with thoracotomy in c-N2 NSCLC. RATS allows a safe and radical procedure also in locally advanced lung cancer, at least when upfront surgery without neoadjuvant treatment is used. The latter needs to be further evaluated. Since safety and radicality are the key elements of all cancer operations, the most important goal is achieved. Secondary factors such as early postoperative pain, drainage time, and intraoperative blood loss favor the minimal-invasive approach by RATS—as previously shown for VATS. As a word of caution, safety and quality of surgery depends heavily on the surgeon's experience and technique and this trial was performed in hospitals with high case volumes und experienced surgeons. They have to be congratulated on their excellent results.

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