

Peer review file

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Reviewer A

The authors reported about the current clinical practice about preoperative histological confirmation of lung cancer in Netherlands. They found that more than one-third of the patients underwent surgical resection without preoperative histological confirmation. The reviewer could know the current situation in the Netherlands, but he could not understand the significant importance/meaning of this study.

General response: we would like to thank the reviewer for the valuable comments. We have attempted to emphasize the importance and consequences of our findings in the background and discussion (page 4, line 73-82 and pages 11-14, line 231-294). In our opinion, the setting where the patient undergoes surgery without preoperative histological confirmation of presumed lung cancer possibly leads to the possibility of unnecessary surgery in cases with an ultimately benign diagnosis. Furthermore, especially for patients with small peripheral tumors, the absence of preoperative diagnosis and histological subtyping could lead to inferior prognosis after sublobar resection. Therefore, our results will serve at least as benchmarking of the current practice.

Minor points:

Comment 1: Regarding Figure 3, what does hospital volume mean? The number of lung cancer? What does Figure 3 mean?

Reply: We thank the reviewer for pointing this out. We have clarified this in the revised version of the manuscript: in the methods section, we now refer to the hospital resection volume as the total number of anatomical parenchymal resections for lung cancer in a hospital. The Statistical analysis section is now revised to explain the method used.

Changes in the text: page 8, line 157-158; page 8, line 162-164 and page 26, line 545-546.

Comment 2: In how many patients did the authors have difficulty in making an

intraoperative diagnosis? How many percentages of intraoperative diagnosis were cytology?

Reply: Unknown, frozen section diagnoses during surgery are not recorded in the NCCR database. Intraoperative diagnosis could be achieved by frozen section or by definitive pathological examination after the surgery. We adjusted the methods section in order to clarify this.

Changes in the text: page 7, line 142-145.

Reviewer B

The authors investigate in a national cancer registry the proportion of patients in whom the diagnosis of lung cancer is secured at the time of surgical resection. The identify this proportion as a quality of care issue in the Abstract Conclusion.

Following a discussion of various guidelines and recommendations in which the authors argue that variations in surgical care are introduced by conflicting guidelines, they study all patients with a pathologic diagnosis of lung cancer who underwent anatomic lung resection in a recent six-year interval in the Netherlands.

They find that 36% of patients had an intraoperative diagnosis of lung cancer, a proportion that decreased with tumor size, was high in adenocarcinoma and small cell carcinoma, and varied with extent of resection.

Multivariable analysis results are mentioned in the Results section, but no table is provided. A “residual variation between hospitals” is mentioned in Results, shown in Figure 3 but is not defined or explained anywhere in the manuscript.

General response: we would like to thank the reviewer for the valuable comments. Regarding the multivariable analysis, the data has been provided in Table 2, but was not clearly noted in the Results section; this will be changed accordingly. Additionally, we agree that “residual variation between hospitals” has not been properly defined and clarified. We have made changes accordingly in the Methods and Results section

Changes in the text: Page 8, 157-164 and Page 10, line 196-201

Comments:

1. Obtaining a preoperative diagnosis in resectable lung cancer is dependent upon many

measurable and unmeasurable variables. The authors focus of course on the measurable variables tumor size, tumor location, postoperative histologic diagnosis and extent of resection. The unmeasurable variables including quality of radiographic interpretation, availability and quality of CT-guided needle biopsy or competence in endobronchial ultrasound depend on local availability and are not necessarily tied to hospital volume. Employing an isolated proportion of intraoperative diagnosis not corrected for measurable variables and not taking into account substitutes for unmeasurable variables as a quality metric is of unclear value.

Reply: we agree to this point and have added text to discussion regarding this.

Changes in the text: page 11-12, line 240-247.

2. Hospitals offering lung cancer screening CTs or lung nodule clinics likely have a greater proportion of smaller cancers. In their reference 13, 40% of all lung cancer diagnosed in a pulmonary nodule clinic were less than 1 cm in diameter, and the vast majority measured less than 2 cm. The rate of preoperative diagnosis was less than 10% in that reference. The same problem noted above will arise when using intraoperative diagnosis as a quality metric.

Reply: We agree with the reviewer's comment that hospitals (and countries) offering lung cancer screening will likely have a greater proportion of smaller cancers. But it is exactly with this anticipated future development that the need to obtain a preoperative diagnosis could become increasingly important. In this regard, reference 13 provides important data: of the 129 patients undergoing surgical resection, indeed <10% received percutaneous needle biopsy preoperatively. However, this diagnostic approach led to 17% "unnecessary surgery" with an ultimately benign diagnosis. Moreover, as stated by the authors themselves, "lobectomy was performed in 3 of 21 (14.3%) benign incidental nodules because their central location precluded a lesser resection". In our opinion, as stated in the discussion (page 11-12, line 240-247), these numbers challenge the physician's ability to make a reliable lung cancer diagnosis solely based on clinical and radiologic data. Therefore, a balance should be found between the unwarranted trauma and morbidity caused by unnecessary surgery, and the possible complications of preoperative invasive diagnostic procedures. We believe that national and international consensus should be sought, beginning with benchmarking our current lung cancer practice, as we have attempted in this national population-based study.

To more clearly elucidate our viewpoint, we have added additional comments on this matter in the Discussion section.

Changes in the text: page 11-12, line 240-247; page 16, line 341-356.

3. The multivariable analysis is not detailed in a separate Table, and it should.

Reply: Regarding the multivariable analysis, the data has been provided in Table 2, but was not clearly noted in the Results section; this will be changed accordingly

Changes in the text: page 10, line 196-201.

4. As noted above, the term “residual variation between hospitals” must be explained, and the legend for Figure 3, as for the other figures, should explain what is shown, independent of explanations in the text. Are the intraoperative diagnosis rates per hospital corrected for differences in disease?

Reply: We agree, statistical session is expanded. Also in the results and the legends of figures we added/adjust the text to be more clear.

Changes in the text: page 8, line 157-158; page 10, line 196-201; page 25, line 542-543 and page 26, line 545-546.

5. A notable observation in this study is the low rate of segmentectomy. When lung cancer is diagnosed early, for example as a small, slow-growing adenocarcinoma, lesser resection should occur more frequently. In the Netherlands, segmentectomy is a rarity. This suggests factors other than disease. Surgeons may not be familiar with the operation if they do lung cancer operations in addition to heart or general surgery. Further, an omission in this study is the lack of data on surgical approach; we are not informed whether thoracotomy or minimally invasive techniques are used. Surgical approach should be considered in this context because minimally invasive techniques are associated with lower perioperative risk and are surrogate markers for surgeons specialized in general thoracic surgery.

Reply: We agree with this. We added text to the discussion regarding this point.

Changes in the text: page 16, line 341-356

Reviewer C

Overall, nice study addressing an increasingly important topic given (as the authors note) the increased use of lung cancer screening and sublobar resection. I congratulate the authors on the manuscript and do believe it will be of significant interest with consideration of the following comments.

The lack of surgery for benign disease is a limitation, but this was appropriately recognized by the authors and I will look forward to future study they indicate on this topic.

However, another major limitation is the lack of data on whether any diagnostic procedure was attempted pre-operatively without successful diagnostic yield. It is quite possible that patients noted to have IOD actually had undergone CT-guided biopsy and/or bronchoscopic procedure prior to surgery with either non-diagnostic results or false negative results. If the NNCR can provide these data I would strongly encourage the authors to analyze and include these data. If the data are unavailable, this topic should be discussed.

I would also like to see more discussion on proposed reasons for the hospitals with significantly different rates of IOD from the national average. Is this felt to be secondary to different diagnostic/treatment algorithms or, perhaps, is this due to increased use of lung cancer screening or lack of available pre-operative diagnostic modalities?

Reply: we thank the reviewer for the valuable comments and we agree to this point and have added text to discussion regarding this. Unfortunately, NCCR does not provide data about the preoperative diagnostic tests. However, future studies by our group will attempt to address these issues on (the variations in) preoperative diagnostic testing in a different national database more focused on surgical details.

Changes in the text: page 16, line 341-356.

Reviewer D

This manuscript presents the first available nationwide population based numbers on IOD rates in patients undergoing lung cancer surgery in the Netherlands.

It is self-evident that advances in diagnostic imaging have led to the discovery of small

lung cancers, which have reduced the preoperative diagnosis rate. And that's not a bad thing in itself. Pulmonologists aren't skipping preoperative diagnoses.

Reply: We would like to thank the reviewer for the valuable comments. We agree with the observation that “that advances in diagnostic imaging have led to the discovery of small lung cancers”, especially in regions and countries with a progressive lung cancer screening program. However, this does not necessarily have to be accompanied by a reduction of a preoperative diagnosis rate. As an example, reference 13 provides important data: of 129 patients undergoing surgical resection with pulmonary nodules found by lung cancer screening or as an incidental finding, 75-80% were <2cm. In this cohort, <10% received percutaneous needle biopsy preoperatively. However, this diagnostic approach led to 17% “unnecessary surgery” with an ultimately benign diagnosis. Moreover, as stated by the authors themselves, “lobectomy was performed in 3 of 21 (14.3%) benign incidental nodules because their central location precluded a lesser resection”. In our opinion, as stated in the discussion (page 11-12, line 240-247), these numbers challenge the physician’s ability to make a reliable lung cancer diagnosis solely based on clinical and radiologic data. Therefore, a balance should be found between the unwarranted trauma and morbidity caused by unnecessary surgery, and the possible complications of preoperative invasive diagnostic procedures. We believe that national and international consensus should be sought, beginning with benchmarking our current lung cancer practice, as we have attempted in this national population-based study.

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