sequencing in a universal health-care setting. Although drawbacks to this approach include sample transport and ensuring standardisation of pre-analytical factors, next-generation sequencing platforms require substantial capital expense, specialised personnel, and a robust bioinformatics infrastructure, which could make a centralised approach faster, more accurate, more scalable, and possibly more affordable. We must also ensure that patients' autonomy and privacy is protected when performing next-generation sequencing.

All stakeholders need to be aware that new and more effective drugs and treatments could be offered to patients only after scientific research and investment has been made to produce high quality data from clinical trials. Additionally, international collaboration and genomic research expertise will improve clinical knowledge and support the development of scientific capacities for next-generation sequencing technologies.

*Marcos Santos, Renata A Coudry, Carlos Gil Ferreira, Stephen Stefani, Isabela Werneck Cunha, Mariano Gustavo Zalis, Luiz H Araujo

UNESCO Chair of Bioethics, Faculty of Health and Sciences, University of Brasilia, CEP 70919-970, Brasilia, Brazil (MS); Anatomic Pathology Department, Hospital Sírio Libanês, São Paulo, Brazil (RAC); D'Or Institute for Research and Education, Rio de Janeiro, RJ, Brazil (CGF); Mãe de Deus Cancer Center, Porto Alegre, Brazil (SS); Pathology Department, Rede D'OR São Luiz, Sao Paulo, Brazil (IWC); Departament of Research and Development, Instituto Hermes Pardini, Vespaziano, Minas Gerais, Brazil (MGZ); Brazilian National Cancer Institute, Rio de Janeiro, RJ, Brazil (LHA); and COI Institute for Education and Research, Rio de Janeiro, RJ, Brazil (LHA).
mrcsantos@unb.br

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Intraoperative lymph-node assessment during NSCLC surgery: the need for standardisation and quality evaluation

Analyses of large contemporaneous national databases, even in the era of modern pre-treatment staging methods, show a 10–20% incidence of nodal upstaging in patients with clinical stage I non-small-cell lung cancer (NSCLC) and treated with lobectomy.[1] Therefore, lymphadenectomy is still heralded as a hallmark of surgical quality. However, this opinion is often poorly adhered to in clinical practice. Similarly, clinical research is not free from low adherence: in the randomised ACOSOG Z4032 trial,[2] which compared sublobar resection alone with sublobar resection and brachytherapy in patients with clinical stage I NSCLC, more than a third of the patients did not receive any kind of lymph node evaluation.[2] International guidelines about what constitutes an adequate nodal dissection differ in their specific requirements, and major intercontinental variation in pathological node status (pN) category-stratified survival has been reported.[3] Even if underlying racial differences in lung tumour biology contribute to this variation, there are also possible disparities related to the aggressiveness of preoperative and intraoperative nodal assessment that lead to differences in outcomes.


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Thoroughness of pathological node examination in surgical cohorts can be accurately assessed as the number of lymph nodes and stations removed, because the use of sequentially more stringent nodal criteria leads to the best prognostic delineations.[4] In patients with pN1–2 NSCLC, the lymph node ratio—the number of positive lymph nodes versus the total number of

resected lymph nodes—can be independently associated with decreased overall survival and time to recurrence, outperforming prognostic models that are based on a combination of anatomical location and number of involved nodes.[5] For individuals, however, these metrics are obviously unsound because of inter-individual and intra-individual variability, which remains a clear obstacle to the application of the sentinel lymph node technique, and potential confounding from the manner of counting lymph node fragments. Furthermore, if the retrieval of hilar and mediastinal nodes depends entirely on the surgeon, that of intrapulmonary nodes inside the operative specimen depends at least partially on the pathologist. Additionally, the information about extracapsular versus intracapsular tumour extension within invaded lymph nodes should be included in the pathology report, because of its prognostic significance and effect on the assessment of the completeness of the resection,[6] which is the primary goal of NSCLC surgery at any stage.

Absences of standardisation in surgical techniques and uniform terminology have compounded the difficulties in assessing the efficacy of intraoperative lymph node evaluation. Systematic lymphadenectomy refers to as complete as possible lymph node removal following established anatomical boundaries. In clinically N0 patients, selective lymphadenectomy and systematic sampling are the only acceptable alternatives. Selective lymphadenectomy refers to lobe-specific nodal dissection, which means removal of interlobar (station 11) and hilar (station 10) lymph nodes by the surgeon, as well as a minimum of three mediastinal stations depending on the tumour location but including subcarinal lymph nodes (station 7) in all cases.[7] However, several historical studies have shown that lobe-specific lymphatic drainage was not exclusive. Systematic sampling refers to examination of predetermined lymph nodes and stations. The largest randomised trial comparing systematic dissection with systematic sampling, the ACOSOG Z0030 trial,[8] showed no difference in overall or disease-free 5-year survival between the two groups. This finding probably results from the selection of patients with small-sized and early-stage tumours for the trial, and highly rigorous lymph node evaluation before randomisation, strengthened by the adjunct of routine frozen sections, which is however rarely applicable in daily practice. The trial gives strong indications on what constitutes minimal information about the lymph node status in patients with a presumed early stage NSCLC, and thereby the default definition of pNx patients whose expected survival approximates that for pN1 disease more closely than that for pN0 disease.[4] Accordingly, at least stations 10, 2R, 4R, and 7 should be sampled during right-sided resections, and stations 10, 5, 6, and 7 during left-sided resections. The trial also showed that there was no additional morbidity associated with systematic dissection.

Better understanding of histological tumour biology led to the 2011 classification of lung adenocarcinoma by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society,[9] which identified patient subgroups with high propensity to spread to lymph nodes, thereby opening a door to some form of tailored or personalised surgery. Indeed, the presence of micropapillary pattern and absence of lepidic pattern have been shown to be clinically significantly associated with unexpected lymph node metastasis in cN0 patients.[9] However, adenocarcinoma represents only 60% of current lobectomy specimens. Moreover, correlations between occult lymph node disease and histological patterns evaluated with either preoperative biopsies or intraoperative frozen section remain to be investigated for clinical decision-making in surgical procedures.

A landmark study based on data from an all-inclusive, prospectively collected national database in Denmark, with nearly 100% follow-up, provided compelling evidence that nodal upstaging occurs less often with video-assisted thoracic surgery than with open lobectomy in patients with clinical stage I NSCLC.[1] The absence of a significant effect of the surgical approach on long-term survival is likely to be due to the limited magnitude of the benefit of a systematic lymph-node dissection in patients with the most favourable prognosis, similar to what is illustrated by the respective survival curves in the ACOSOG Z0030 trial that compared systematic dissection with systematic sampling.[8] Similarly, we can no longer ignore the accumulating evidence showing that small-sized tumours, performance of sublobar resections, and use of minimally invasive approaches expose the patient to inadequate lymph node sampling according to International Association for the Study of Lung

Cancer recommendations, even in high-volume tertiary academic centres.[10] This trend runs the risk of being regarded as part of the emerging paradigm of so-called precision surgery. Indeed, the legitimate quest for less invasive surgery should not trigger the imperative needs to standardise surgical techniques and to stick to fundamental principles of lung cancer treatment. Surgeons should never lose sight of this fact, and should track adherence to these principles of radicality to assess the quality of surgery, either in daily practice or clinical research, especially when debating the use of alternative ablative therapies or multimodal treatment strategies with or without surgery.

Pascal-Alexandre Thomas
Department of Thoracic Surgery, North Hospital, Aix-Marseille University & Assistance Publique-Hôpitaux de Marseille, 13915 Marseille, France; Predictive Oncology Laboratory, Centre de Recherche en Cancérologie de Marseille, Inserm UMR1068, CNRS UMR7258, Aix-Marseille University UM105, Marseille, France
pathomas@ap-hm.fr

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