Review Article

Multiple pulmonary nodules: a management dilemma

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Abstract: The management of patients with multiple pulmonary nodules is increasingly common, representing diagnostic and therapeutic challenges. The various presentations of synchronous versus metachronous appearance, ipsilateral versus contralateral manifestation, central *vs.* peripheral location, and separate primary etiology versus T3, T4, or M1 status contribute to the complexity of the decision-making, including the timing of resection, the extent of resection, and the use of systemic therapy. The goal of the evaluation is complete preoperative staging to determine oncologic operability; physiologic operability must also be assessed, which may guide the use of lobar *vs.* sub-lobar resection. Even after resection, it may not be clear whether the multiple malignancies represent separate primaries or more advanced involvement: T3, T4, or M1a. The algorithmic approach to evaluation and management supports the use of resection even in cases of T4 or M1a disease, in conjunction with systemic therapy, in the absence of other metastatic diseases. The presence of N1 or N2 nodal disease is an additional factor that further complicates decision-making, both the extent of resection and the use of systemic therapy. In this chapter we will summarize different criteria used to stage multifocal lung nodules and discuss algorithms for surgical management, including our practice at Duke Cancer Institute.

Keywords: Lung cancer; multi-focal lung cancer; sub-lobar resection

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With the widespread use of thoracic imaging in multiple clinical settings, including but not limited to lung cancer screening and surveillance, small asymptomatic pulmonary nodules are being incidentally discovered more and more frequently. In a systematic review of 8 lung cancer screening studies, 8% to 51% of imaging studies demonstrated at least one pulmonary nodule, with more than one nodule identified in many (1). Despite recent advances in surveillance algorithms, diagnosis and treatment strategies for solitary pulmonary nodules, the presence of multiple pulmonary nodules remains a diagnostic and management dilemma.

The increased usage of thin-sectioned computed tomography (CT) has also led to the increased incidence of discovering ground-glass opacities (GGO), also termed ground glass nodules, in the lungs. Multiple GGOs incidentally found on imaging might be due to a recent pulmonary infection, or multifocal adenocarcinoma. GGO-dominant lung cancer has the tendency to present in a multifocal fashion (2). In the spectrum of lung adenocarcinoma, the presence of GGO is most often associated with the presence of adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma (MIA), but sometimes may represent less indolent histologies. In this submission, we outline modern strategies for the evaluation and management of patients with multiple solid pulmonary nodules, with the goals of improving the efficiency of the evaluation and minimizing the risks of management,

including over-scanning and over-treating.

Multi-focal lung cancer: separate primary tumors or metastatic disease?

The complexity of the paradigm of multi-focal lung cancer increases with the number of multiple solid nodules. In this situation, three key questions need to be addressed:

(I) Are these nodules benign or malignant?

If malignant:

(II) Are these nodules separate primary lung cancers *vs.* Metastatic or recurrent primary lung cancer?

(III) Are these nodules metastatic lesions from extra-pulmonary carcinoma?

Metachronous presentation refers to the detection of a lung nodule in the setting of previous lung cancer. Clinical correlation contributes significantly to the management process, including a patient's history of previous cancer diagnosis. Lung cancer surveillance programs have been created to help diagnose second primary cancers at an early stage, which significantly increases survival compared to the treatment of more advanced stages. The incidence of metachronous second primary lung cancers after treatment of a previous primary is estimated to be 1% to 2% per patient per year (3).

Synchronous presentation of 2 nodules, each less than 3 cm in diameter, is usually a more challenging clinical situation. This presentation can fall into one of four classifications:

(I) Separate primaries (synchronous in this scenario) correlate with T1 or T2 status.

(II) Lung cancer with metastasis to the same lobe correlates with T3 status (this scenario does not usually present a dilemma as it does not usually influence decision making regarding resection).

(III) Lung cancer with metastasis to separate ipsilateral lobe, which correlates with T4 status.

(IV) Lung cancer metastasized to the contralateral lung, would be designated as M1a disease (4). While it is sometimes possible to obtain a pathologic diagnosis of both nodules in advance of treatment, often decision-making must be founded on clinical judgment and multidisciplinary review.

Martini and Melamed developed clinicopathologic criteria that have been traditionally used to differentiate multiple primary lung cancer and metastatic lung cancer (5).

For synchronous multiple lung cancers, tumors are considered separate primaries if:

- ❖ The tumors are physically distinct and separate, and
- ❖ The histological type is either
  - Different, or
  - Same, but in a different segment, lobe, or lung, and:
    - Origin from carcinoma *in situ;*
    - No carcinoma in common lymphatics;
    - No extrapulmonary metastases at the time of diagnosis.

For metachronous multiple lung cancers, tumors are considered separate primaries if:

- ❖ They are histologically different, or
- ❖ If histologically identical
  - Disease-free interval between cancers ≥2 years, or
  - Origin from carcinoma *in situ*, or
  - Second cancer in different lobe or lung, but:
    - No carcinoma in common lymphatics;
    - No extrapulmonary metastasis at the time of diagnosis.

Antakli *et al.* published a modification of these criteria to differentiate between second or multiple primary lung cancers and recurrence or satellite nodules (6).

- ❖ Different histological conditions;
- ❖ Same histological condition with two or more of the following:
  - Anatomically distinct;
  - Associated premalignant lesion;
  - No systemic metastasis;
  - No mediastinal spread;
  - Different DNA ploidy.

However, these classifications do not include the WHO 2015 classification or molecular analysis that is routinely done for lung adenocarcinoma.

In 2003, the American College of Chest Physicians (ACCP) guidelines proposed modified criteria to differentiate between multifocal lung cancer, pulmonary metastasis, and multiple primary lung cancer (7).

Their criteria were as follows:

(I) T3 tumors (multi foci): same lobe as primary tumor and same histology;

(II) T4 tumors (multi foci): different ipsilateral lobe from primary tumor, and anatomically separated, and same histology;

(III) Pulmonary metastasis: same histology and multiple systemic metastases;

(IV) Or same histology in different lobes and presence

of N2, N3 involvement;
(V) Or <2-year interval;
(VI) Multiple lung cancer: same histology, tumor in different lobe as primary, and no N2, N3 involvement, and no systemic metastases;
(VII) Or different histology, molecular genetic characteristics or arising from a separate focus on carcinoma *in situ*;
(VIII) Or same histology, temporarily separated and ≥ 4-year interval between cancers and no systemic metastases.

In 2015, a subcommittee of the International Association for the Study of Lung Cancer (IASCLC) Staging and Prognostic Factors Committee conducted a systemic review to develop recommendations to identify second primary lung cancers (8). Their review discussed knowledge related to three main topics, which were: mechanism of metastasis, determination of clonality, and outcomes of patients with resected tumors.

Regarding metastasis, the mechanism cannot be simply explained by mechanical dissemination of the tumor by hematogenous and lymphatic spread, suggesting that the actual mechanism of metastasis is too complex to be used to classify lung tumors (8). To determine the clonality of a tumor, the authors studied histologic type, histologic subtype, biomarker pattern, and genetic characterization. Determining that two tumors are different is clearly easier than determining that they are of the same lineage. The only situation where routine assessment is reliable to define clonality is when tumors have a different histology or appear different on a detailed histologic assessment of tumor subtypes and stromal features. All the other criteria that are suggestive of clonality are not necessarily confirmatory, such as: imaging characteristics, presence or absence of nodal involvement, identical histology, and similar biomarkers (8). The response to treatment has been briefly mentioned as part of the clinical evaluation to help distinguish between these entities. As expected, synchronous stage I lung cancer would have better overall survival compared to oligometastatic disease and would not be associated with rapid appearance of distant metastasis. The development of advanced techniques such as next-generation sequencing and comparison of exact breakpoints in gene rearrangements can provide better tools to aid in resolving this controversy.

With respect to GGO tumors, the IASLC committee concluded that a detailed histologic or genomic assessment was not necessary; these lesions should be classified as multifocal adenocarcinoma and viewed as separate primary cancers (8). This decision was based on several factors, including excellent clinical outcomes even in the multifocal setting: the 5-year survival is at least 85% in multifocal GGOs, the incidence of distant metastasis is low (8). This discussion will continue to focus on small solid pulmonary nodules.

Since the identification of specific oncogenic mutations has been suggested in numerous studies as a promising tool to differentiate separate primary tumors from metastatic disease, Asmar and colleagues conducted a study on patients who presented with synchronous and metachronous adenocarcinomas (9). They selected a panel of oncogenic mutations that would potentially be discriminatory—EGFR expression, KRAS expression, ALK receptor tyrosine kinase gene expression, and BRAF expression—and compared this panel in a group of patients in their primary lung adenocarcinoma and a metastatic extra-pulmonary lesion (in patients known to have metastatic disease). The concordance rate between the primary tumors and the metastatic lesions in this cohort was 96%. They hypothesized that this approach could be used to differentiate between multiple primary lung cancer and intrapulmonary metastasis. In the second cohort of patients with multiple lung cancers, 36% of same-lobe nodules were determined to be multiple primary lung cancers (not T3 lesions), and 82% of multiple-lobe nodules were multiple primaries. The overall survival at four years was 80%, supporting the use of these oncogenic mutations and the conclusion that the majority of multiple lung cancers in this series were separate primary tumors (9).

Next generation sequencing (NGS) has also been studied as a more accurate molecular analysis to differentiate multiple primaries from metastatic lung cancer. An algorithm using histo-molecular testing was proposed by Mansuet-Lupo *et al.* to classify tumors are multiple primary lung cancer or metastasis (10). Molecular mutations were identified by NGS in 91% of tumor pairs. Concordance between histologic and molecular classifications was reported in 72% of the patients. The discordant cases were re-classified using the histo-molecular algorithm. After surgical resection, there was no significant difference in survival, suggesting that aggressive surgical management is of benefit even if oligometastatic disease is suspected. However, classifying tumors as multiple primary lung cancer or oligo-metastatic cancer has a significant impact in addressing the need for adjuvant treatment (10).

Clinical decision-making

Even if the analysis of the entire panel of oncogenic mutations or NGS were more commonly available adjuncts to pathologic assessment, clinical decision-making in patients with clinical or pathological multi-focal lung cancer—defined for this discussion as the presence of 2 nodules that are known or suspected lung cancer—would still be challenging. As it is often difficult to obtain a pathologic diagnosis in both nodules prior to treatment, clinicians must rely on informed clinical judgment and algorithms, such as those in the National Comprehensive Cancer Network (NCCN) guidelines (11).

Upon presentation with multiple solid pulmonary nodules (<3 cm) on imaging, the patient should be carefully assessed by a focused history and physical examination. Previous imaging, if available, should be reviewed. CT scan of the chest and upper abdomen should be obtained if the index abnormality was seen on a plain chest radiograph. Obtaining a tissue biopsy to confirm malignancy in at least one nodule is highly preferred for nodules in separate lobes, as multiple resections would be required.

Once malignancy is confirmed, a rigorous evaluation should be performed to complete clinical tumor staging, in addition to the assessment of the patient's fitness for surgery. The work-up includes: a complete set of pulmonary function tests including diffusion, bronchoscopy, pathologic mediastinal evaluation when indicated, brain MRI with contrast, and positron emission tomography (PET) scan (11). It is recognized that PET scan is often obtained prior to biopsy in order to guide decision-making regarding which nodule to biopsy, or to guide biopsy of potential metastatic disease. As well, in some clinical situations, primary resection may be performed prior to biopsy, if the lesions are located such that biopsy would be difficult, if biopsies have been unsuccessful, or in patients in whom the risk of malignancy is high and diagnostic wedge resection followed by definitive anatomic resection would be straightforward.

The goal of the preoperative evaluation is to complete the clinical staging in order to identify operable patients, which would include: separate pulmonary nodules in the same lobe, (T3, N0-1); separate nodules in ipsilateral lobes (T4, N0-1); separate nodules in contralateral lobes (N0, M1a); or, separate primary lung cancers, either ipsilateral or contralateral (T1-2, N0-1). Patients with multifocal lung cancer in the setting of N2/N3 or extra-thoracic metastatic disease should be considered inoperable, and management is beyond the scope of this chapter (11).

The treatment of separate pulmonary nodules in the same lobe (T3) is surgical resection: usually minimally invasive lobectomy and mediastinal lymph node dissection, followed by adjuvant chemotherapy for patients who are staged as T3 or N1, but not those with separate primaries that are T1-2N0. In a small fraction of patients, such as those who have undergone previous resection(s) or those with significantly compromised pulmonary function, sublobar resection may be employed, although single segmentectomy is unlikely to be effective for multiple intralobar solid lesions (11).

For patients with ipsilateral nodules in different lobes (T4), surgical resection with mediastinal lymph node dissection should be performed with attempt to avoid pneumonectomy. On the right side, 2 lobectomies (upper + middle or lower + middle) might be chosen if both nodules are central; however, performing sub-lobar resection for at least one of the nodules, if oncologically appropriate, should also be considered. For patients that are T4 or N1, adjuvant chemotherapy should be offered (11).

If stage IVA (N0, M1a) is suspected (2 contralateral nodules), NCCN guidelines recommend proceeding with staged curative-intent resections, treating the lesions as two primary lung cancers if both are resectable (even if the histology of both tumors is similar). In this situation, it may be prudent to utilize sublobar resection for one of the nodules, if oncologically appropriate. As well, the timing of chemotherapy could be modified to be given as induction therapy, either before both resections or before the second resection, testing the biology of tumor prior to committing the patient to two resections. The decision regarding which nodule to remove first is complex. If one of the planned procedures is segmentectomy, beginning with that side allows for the second procedure to be performed with nearly full contralateral lung function for the second procedure. If both procedures are planned as lobectomy, removing the larger tumor is preferred (11).

In patients with bilateral lesions who are asymptomatic and have a small (<1 cm) contralateral lesion or even multiple other low risk lesions, surveillance with CT scans of the chest may be employed after resection of the primary tumor. If all the lesions are <1 cm and biopsy is not feasible, surveillance may be used as well, according to lung cancer screening algorithms. The frequency of obtaining the scans depends on the largest lesion and may be based on the NCCN(11) or Fleischner guidelines (12).

For small but growing lesions, especially if avid on PET,

definitive therapy may be undertaken, even if biopsy is still not possible. For some patients, parenchyma sparing resection, radiation, or image guided thermal ablation may be options, although minimally invasive resection is associated with the best outcomes (11).

Surgical procedures

Multiple studies have compared lobectomy to sublobar resection for the treatment of lung cancer. Speicher and colleagues compared lobectomy to sublobar resection for clinical stage IA non-small-cell lung cancer (NSCLC) from the National Cancer Database (NCDB). In the sublobar resection group, 84.7% underwent wedge resection and 15.3% underwent segmentectomy. Lymph node evaluation was performed in only 28.8% in the sublobar resection patients. Patients treated with lobectomy had significantly better 5-year survival compared to sublobar resection. In the sublobar resection group, lymph node sampling was associated with significantly better 5-year survival (13). Other studies have recommended that segmentectomy is suitable for clinical stage IA adenocarcinoma and yielded similar recurrence free survival and overall survival as lobectomies (14). Lobectomy, segmentectomy and wedge resection were compared for resecting ≤2 cm GGO with a consolidation/tumor ratio ≤0.25 based on CT. The 5-year disease free survival and 5 year overall survival were not significantly different between the three resection modalities (15).

To help identify the criteria for wedge resections that can be suitable for early NSCLC treatment, Ajmani *et al.* conducted a study where they compared high quality wedge resection (negative margins, >5 nodes) *vs.* average quality (negative margins, ≤5 nodes) *vs.* poor quality (positive margins) *vs.* radiation treatment. High-quality wedge was associated with a lower risk of death compared with average-quality resection. Compared with stereotactic radiation, wedge resection with negative margins had significantly reduced hazard of death regardless of the number of lymph nodes resected. There was no significant survival difference between margin-positive wedge and radiation (16). Two large randomized controlled trials are undergoing to provide better evidence regarding the benefit or harm of sublobar resections in the treatment of lung cancer, JCOG 0802 and CALGB 140503.

Even though lobectomy is the standard of care for most patients with NSCLC (>1 cm), performing multiple lobectomies in patients with multifocal lung cancer might not serve them well, as they might require future resection(s) as well. Thus, complete resection while preserving as much parenchyma as possible should be the aim in patients with multi-focal disease.

NCCN guidelines (11) suggest that the following criteria should be met for the cancer to be resected by a sublobar resection (segmentectomy is preferred):

- Parenchymal resection margins ≥2 cm or ≥ the size of the nodule.
- Appropriate sampling on N1 and N2 lymph nodes for frozen section to confirm clearance of malignant involvement.
- Poor pulmonary reserve, multiple synchronous or metachronous resections, or frail patients with multiple comorbidities.
- Peripheral nodules that are ≤2 cm in diameter with at least one of the following:
  - Pure AIS histology;
  - Nodule has ≥50% ground glass appearance on CT scan;
  - Radiologic surveillance confirms a long doubling time (≥400 days).

For synchronous bilateral lesions, sublobar resection of the smaller lesion first allows the second operation to be better tolerated with single lung ventilation. For unilateral lesions, mediastinal lymph node dissection first is preferable to ascertain the absence of N2 disease. If concerns about residual lung function arise, whether before or after resection of other pulmonary nodules, stereotactic body radiation therapy (SBRT) for smaller lesions can be considered.

Despite the fact that differentiating synchronous primary lung cancer and metastasis is difficult, outcomes after resecting synchronous lung cancer have shown positive results. This has been shown in a study where the patients underwent staged bilateral resections of synchronous lung cancer after excluding N2 disease by invasive mediastinal staging, and after excluding distant metastasis. In this study, 96% underwent at least unilateral thoracoscopic approach, and 60% had bilateral thoracoscopic approach. There was low risk of morbidity. The survival was not related to whether histology was different or the same in resected cancers, suggesting that most of the same-histology nodules were separate primaries, as opposed to metastases. It was concluded that aggressive surgical treatment is advised for synchronous lung cancers (17).

In another study, patients who had bilateral multiple primary lung cancers based on Martini-Melamed criteria

underwent bilateral resections. In this study, 39 patients underwent bilateral lobectomies, 49 patients underwent lobectomy and sublobar resection, and 13 patients underwent bilateral sublobar resections. Overall survival 5 years was 75%. Sublobar resection for contralateral nodule (stage I) did not have a negative effect on 5-year survival. Most of the sublobar resections were wedge resections with lymph node sampling. Multivariate analysis showed that most advanced tumor, node, metastasis (TNM) stage and the number of lesions as significant predictors of overall survival. Their main conclusions were that surgical resection for bilateral multiple primary lung cancer showed promising results, sublobar resections did not negatively affect the survival, and there was good correlation between post-operative pathologic staging and prognosis in these patients. Patients with different post-operative histology had slightly better overall survival than patients who had similar histology, but the difference was not statistically significant (18).

Summary

Multifocal lung cancer represents a difficult management dilemma, and the incidence of this paradigm is increasing. In patients with 2 known or suspected lung cancers, the management should follow established clinical algorithms and multi-disciplinary evaluation and discussion. The preoperative evaluation should be thorough, with the recognition that the presentation of 2 solid pulmonary nodules possibly represents 2 primary tumors, T3 or T4 cancers, or M1a disease, and pathologic mediastinal staging, PET and brain imaging should be considered mandatory (although the presentation may also be consistent with 2 early-stage cancers). Surgical resection should be considered strongly if oncologically and physiologically feasible, and sub-lobar resection should be considered if oncologically appropriate.

In our practice at the Duke Cancer Institute, for patients with 2 known or suspected lung cancers, complete preoperative staging (including pathologic mediastinal lymph node analysis), is performed prior to resection, and preoperative biopsy performed if feasible. For T3 tumors lobectomy, mediastinal lymph node dissection and adjuvant chemotherapy is performed, with consideration of using adjuvant therapy for tumors larger than 4 cm in diameter or in patients with other high-risk factors. For T4 tumors, lobectomy for the dominant lesion and sub-lobar resection of the smaller nodule is most often is performed; if both lesions are central or if tumor size contraindicates sublobar resection, pneumonectomy is performed if physiologically feasible. Induction or adjuvant chemotherapy is also administered.

For patients with bilateral lesions, lobectomy for the dominant lesion and sub-lobar resection of the smaller nodule is most often is performed in staged procedures. Chemotherapy may be delivered before the first resection, before the second resection, or after the second resection. Finally, in patients in whom 2 operations are planned, we often perform the less complex procedure first, to facilitate single lung ventilation during the second procedure. In patients in whom one of the nodules is <1cm in diameter, surveillance of this nodule may be performed prior to a decision regarding resection.

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References

1. Wahidi MM, Govert JA, Goudar RK, et al. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:94S-107S.
2. Kim TJ, Goo JM, Lee KW, et al. Clinical, pathological and thin-section CT features of persistent multiple ground-glass opacity nodules: comparison with solitary ground-glass opacity nodule. Lung Cancer 2009;64:171-8.
3. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. J Natl Cancer Inst 1998;90:1335-45.
4. Lim W, Ridge CA, Nicholson AG, et al. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. Quant Imaging Med Surg 2018;8:709-18.
5. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
6. Antakli T, Schaefer RF, Rutherford JE, et al. Second primary lung cancer. Ann Thorac Surg 1995;59:863-6; discussion 867.
7. Kozower BD, Larner JM, Detterbeck FC, et al. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-99S.
8. Detterbeck FC, Franklin WA, Nicholson AG, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:651-65.
9. Asmar R, Sonett JR, Singh G, et al. Use of Oncogenic Driver Mutations in Staging of Multiple Primary Lung Carcinomas: A Single-Center Experience. J Thorac Oncol 2017;12:1524-35.
10. Mansuet-Lupo A, Barritault M, Alifano M, et al. Proposal for a Combined Histomolecular Algorithm to Distinguish Multiple Primary Adenocarcinomas from Intrapulmonary Metastasis in Patients with Multiple Lung Tumors. J Thorac Oncol 2019;14:844-56.
11. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw 2021;19:254-66.
12. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology 2017;284:228-43.
13. Speicher PJ, Gu L, Gulack BC, et al. Sublobar Resection for Clinical Stage IA Non-small-cell Lung Cancer in the United States. Clin Lung Cancer 2016;17:47-55.
14. Tsutani Y, Miyata Y, Nakayama H, et al. Oncologic outcomes of segmentectomy compared with lobectomy for clinical stage IA lung adenocarcinoma: propensity score-matched analysis in a multicenter study. J Thorac Cardiovasc Surg 2013;146:358-64.
15. Ha KJ, Yun JK, Lee GD, et al. Surgical Outcomes of Radiographically Noninvasive Lung Adenocarcinoma according to Surgical Strategy: Wedge Resection, Segmentectomy, and Lobectomy. Korean J Thorac Cardiovasc Surg 2018;51:376-83.
16. Ajmani GS, Wang CH, Kim KW, et al. Surgical quality of wedge resection affects overall survival in patients with early stage non-small cell lung cancer. J Thorac Cardiovasc Surg 2018;156:380-391.e2.
17. Shah AA, Barfield ME, Kelsey CR, et al. Outcomes after surgical management of synchronous bilateral primary lung cancers. Ann Thorac Surg 2012;93:1055-60; discussion 1060.
18. Yang H, Sun Y, Yao F, et al. Surgical Therapy for Bilateral Multiple Primary Lung Cancer. Ann Thorac Surg 2016;101:1145-52.

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