Title: The Evolution of the Treatment of Non-small Cell Lung Cancer: A Shift in Surgical Paradigm to A More Individualized Approach

Short Running Title: Lesser Resection but More Lung-sparing for NSCLC

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Central Message: A surgical paradigm to a more individualized approach for small NSCLC has evolved over the last decades with evidence demonstrating improved prognosis.

Perspective Statement: The shift in the spectrum of lung cancer facilitates a lung-sparing individualized approach.

Central Picture Legend: Evolving guidelines for the surgical strategy of NSCLC.
Abbreviations
NSCLC: non-small cell lung cancer; LND: lymph node dissection; GGO: ground-glass opacity;
HRCT: high-resolution computerized tomography; LUAD: lung adenocarcinoma; CTR: consolidation-to-tumor ratio; TSCT: thin-section CT; JCOG: Japan Clinical Oncology Group;
IASLC: International Association for the Study of Lung Cancer; ATS: American Thoracic Society;
ERS: European Respiratory Society; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; FS: frozen section; FP: final pathology; IAC: invasive adenocarcinoma; AAH: atypical adenomatous hyperplasia; RFS: recurrence-free survival; OS: overall survival; SPLC: second primary lung cancer; DFS: disease-free survival; NLST: National Lung Screening Trial;
ECTOP: Eastern Cooperative Thoracic Oncology Project

Abstract
Surgical treatment is an integral part of the comprehensive therapeutic methods for lung cancer, especially for early-stage non-small cell lung cancer (NSCLC). With a deeper understanding of the disease, we found that lung cancer is more commonly detected in young females. For regions of Asia, more lung cancer has been detected in early-stage GGO-dominant non-smokers. Therefore, surgical strategies have also been reformed commensurate with the shift of the disease spectrum. However, the pursuit of lung-sparing individualized approaches has raised worldwide attention.
Suitable surgical treatment within the curative time window is recommended to maximize the long-term benefit. This article summarizes the shift in surgical treatment for small NSCLCs and hopes to enlighten further innovations to fill in the gaps between the unmet needs and a more individualized approach.

Keywords: lung cancer; surgical treatment; early-stage; minimal invasive surgery
Introduction

Lung cancer is the most commonly diagnosed cancer in men and the leading cause of cancer-associated mortality in both men and women \(^1\). Up to 85% of lung cancer cases are non-small cell lung cancer (NSCLC) \(^2\). Among the newly diagnosed NSCLC each year, approximately one-third are in the early stage of clinical evaluation and typically undergo surgery for curative-intent resection \(^3,4\). Since the early last century, there has been a shift in the surgical management for early-stage NSCLC especially in the past three decades with the changes of the NSCLC spectrum. In this review, we summarize the shift mainly chronologically (Fig. 1) and conclude with a brief overview of the future perspectives in the surgical management of early-stage NSCLC.

Historical Timeline of Surgery

The first milestone of successful one-stage pneumonectomy was performed in 1933 by Evarts A. Graham for a patient with a squamous cell carcinoma in the left upper lobe of the lung with tumor involvement of the left lower lobe bronchus \(^5\). At that time, it was believed that a sufficiently large extent needed to be excised regardless of the size and location of the tumor. Therefore, pneumonectomy became the standard surgical procedure for lung cancer surgery until the 1950s.

In 1950, Churchill et al. \(^6\) reported that lobectomy induced a significantly longer 5-year overall survival (12% vs. 19%) and less mortality (22.8% vs. 14%) compared to pneumonectomy. Surgeons realized that lobectomy with enough margin could be the right choice for some patients. Bronchoplastic and angioplastic procedures emerged to avert pneumonectomy, especially in those in old age or with poor cardiovascular function. In 1951, Cahan et al. \(^7\) proposed “radical pneumonectomy” which added hilar and mediastinal (regional) lymph node dissection (LND).
Nine years later, in 1960, Cahan et al.\textsuperscript{8} reported the results of the patients who underwent “radical lobectomy”, which gradually became a standard anatomic resection for lung cancer patients to improve operative mortality as well as preserve more lung parenchyma later on\textsuperscript{9}.

In 1976, a study by Paulson et al.\textsuperscript{10} investigated the postoperative survival of 249 patients in three time periods: 1945-49, 1950-59, and 1960-69. The strategy for managing lymph nodes was different after 1960 when LND was put into practice. However, the 5-year survival rates of 6\% and 8\% for stage III patients in the 1950s and 1960s showed no significant benefit from LND. Therefore, with little influence on patient prognosis, LND was not routinely recommended. In the following decades, elaborated routes of lymphatic drainage were gradually reported.

Considering early-stage peripheral NSCLC, there was a debate on whether lobectomy or limited lung resection was more suitable for this cohort\textsuperscript{11-13}. The first segmentectomy was documented in 1973 as an intentional curative procedure for primary lung cancer\textsuperscript{13}, which included 123 segmentectomies on 119 patients over the past 15 years and challenged the standard of lobectomy at that point. Therefore, researchers believed that for lung cancer patients with poor cardiopulmonary function reserve, segmentectomy was more suitable. However, at that time, small-sized lung cancer could be easily missed in chest radiography due to the low resolution. In the 1980s, the wide implementation of CT in lung cancer facilitated the detection of smaller nodules. Surgeons felt obligated to perform limited resections to preserve normal lung parenchyma as much as possible for the patients. In 1995, a prospective randomized clinical trial conducted by the Lung Cancer Study Group compared the effect of lobectomy versus limited resection in 247 patients with stage I peripheral NSCLC was published\textsuperscript{14}. Due to the higher mortality (30\% increase)
and higher local recurrence (tripling increase) brought by limited resection, lobectomy since then has been consolidated to be the gold standard of surgical management \(^{14}\).

### Recent Advances in Surgical Strategy

In the last three decades, the advent of ground-glass opacity (GGO) visualized by high-resolution computerized tomography (HRCT) screening brought forth the surging number of GGOs detected and has aroused worldwide attention. In 1989, from the findings in HRCT, Gamsu et al. \(^{15}\) first illustrated “hazy increased CT density”, which was believed to be a sign of an active inflammatory process. In 1991, the term “GGO” was adopted to represent nonspecific radiologic findings, including alveolar proteinosis, idiopathic pulmonary fibrosis, extrinsic allergic alveolitis, or desquamative interstitial pneumonia \(^{16}\). It was in 1996 that Jang et al. \(^{17}\) proposed focal GGO be an early sign of lung adenocarcinoma (LUAD). Considering the latest and generally acknowledged classification of GGO, they were divided into pure GGO and part-solid nodules \(^{18-21}\). Parameters including consolidation-to-tumor ratio (CTR) were used to measure the solid proportion of GGO \(^{20-23}\).

According to retrospective studies, researchers believed that preoperative thin-section CT (TSCT) images of GGOs could well predict LUAD patients' invasiveness and nodal status \(^{24-31}\) and that CTR \(< 0.50\) was proposed to be one of the most promising definitions to predict the “early” stage. Limited resection avoiding LND was considered fine for this group of patients. Therefore, the Japan Clinical Oncology Group (JCOG) Lung Cancer Surgical Study Group conducted a series of clinical studies hoping to set radiological criteria to predict pathological noninvasiveness before surgery (Fig. 2). The pros and cons of existing trials are also summarized in Table.
As the pioneering work, the prospective observational study JCOG0201 recruited 543 patients from 2002 to 2004 to define the radiological criteria on TSCT that could be used to preoperatively predict the pathological invasiveness of clinical T1N0M0 peripheral lung cancer. The primary goal of this study was not statistically confirmed in the end. Subgroup analysis found that if the radiological non-invasive cutoff value was a lesion diameter of $\leq 2.0$ cm and CTR $\leq 0.25$, the specificity in predicting pathologically non-invasive adenocarcinoma of tumors (absence of lymph node metastasis and vascular invasion in postoperative pathology) reached 98.7%, but the accuracy was only 38.8% \cite{32,33}. This cutoff value only avoids the undertreatment. Based on the results of JCOG0201, a series of JCOG clinical studies was launched in 2009 aiming to further investigate the efficacy and safety of sublobectomy for radiologically invasive or non-invasive peripheral GGO-featured lung cancer (Fig. 2).

In 2011, the new classification of LUAD was proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) \cite{34}, in which the categories of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) came forth and were deemed to be pre- and minimally invasive pathologic stages of LUAD. Zhang et al. \cite{35} confirmed the noninvolvement of lymph nodes in specific tumor histologies including AIS and MIA. Therefore, based on the diagnosis of intraoperative frozen-section (FS) pathology, wedge resection has been performed for small-sized peripheral LUADs since 2011 \cite{36}, and the concordance rate of intraoperative FS with final pathology (FP) in differentiating invasive adenocarcinoma (IAC) from atypical adenomatous
hyperplasia (AAH)/AIS/MIA was 95.9%. While 43.1% of the patients underwent wedge resection and 10.7% underwent segmentectomy, the 5-year recurrence-free survival (RFS) of AIS/MIA after wedge resection and IAC after major resection was successfully stratified by intraoperative FS (100% vs. 74.1%). The post hoc retrospective study by Zhang et al. showed that whereas 6.3% of the patients confirmed an upgraded diagnosis from the final pathology, wedge resection guided by intraoperative FS is still adequate for FS-underestimated IAC, with a 5-year RFS being 100%. Thus, it is plausible for FS to guide the resection strategy for peripheral small-sized LUAD effectively to endeavor lung-sparing individualized approaches. To distinguish the role of FS, it is noteworthy that the FS we mentioned here was used solely for tumor diagnosis.

The 10-year follow-up study by Yotsukura et al. and Li et al. confirmed the perfect 10-year RFS (100%) of the patients with AIS/MIA after surgery. Notably, lobectomy accounted for a significant proportion (56.3% and 36.8%, respectively), which viewed from today's perspective, could be less lung-sparing for this proportion of patients. It may be excessive to perform resections that will not spare lung parenchyma when a lesser resection would suffice, such as a lobectomy over a sublobar resection. The same sentiment could be made regarding the performance of a LND when it may not be necessary.

JCOG0804/WJCOG4507L

For radiologically non-invasive lung cancer, the single-arm clinical study JCOG0804/WJCOG4507L was launched in 2009 to further investigate the efficacy and safety of wedge resection (n = 258) and segmentectomy (n = 56). However, it was not until 2022 that the results came out. The 5-year RFS reached 99.7% without local recurrence. The 10-year RFS
and overall survival (OS) rates were 98.6% and 98.5%, respectively. According to the new classification of LUAD, the predictive accuracy of the JCOG0201 criteria was only 62.2%, while the counterpart for intraoperative FS diagnosing AIS/MIA was 96.1%. On the one hand, owing to the excellent 5-year RFS for IAC (99.1%) in JCOG0804, sublobectomy did not cause undertreatment for the invasive LUAD. On the other hand, however, people were blindfolded by the good prognosis and failed to notice the inadequate predictive accuracy of the JCOG0201 criteria, until the release of the JCOG1211 result.

JCOG1211

The multicentre single-arm study JCOG1211 was launched in 2013 and evaluated the surgical efficacy and safety of segmentectomy for the “radiologically invasive” tumors (tumor ≤ 2.0 cm with a CTR between 0.25 and 0.50; tumor between 2.0 cm and 3.0 cm with a CTR ≤ 0.50)\(^\text{43}\). The 5-year RFS was 98.0% for the whole group. According to a new classification of LUAD, the diagnostic accuracy of invasiveness for this group of patients was only 42%. The remaining 58% of the patients were pathologically confirmed as AIS/MIA. In this group of patients except for 11% of non-peripheral tumors with a diameter ≤ 2.0 cm and a CTR ≤ 0.25, segmentectomy had to be done due to the unamenability to wedge resection due to anatomic location within the lobe or thorax, while 47% of the patients could have received wedge resection, preserved more pulmonary function and preserved the hilar structure intact. Hence, JCOG1211 revealed its unsatisfying predictive accuracy of the invasiveness of small tumors with 0.25 < CTR < 0.50, which induced less lung-sparing of applying segmentectomy for AIS/MIA patients who could have received wedge resection. The perfect prognosis of AIS/MIA after surgery strengthened the clinical significance of distinguishing AIS/MIA from IAC and advert more extensive procedures.
Additionally, according to Yotsukura et al.\textsuperscript{38}, the estimated incidence rate of metachronous second primary lung cancer (SPLC) at 10 years after resection was 5.6\% and 7.7\% for AIS and MIA, respectively, with the median interval between the initial surgery and the occurrence of SPLC being 87 months and 97 months, respectively. Likewise, in the study by Li et al.\textsuperscript{39}, the 10-year postoperative incidences of developing SPLC for patients with AIS and MIA were 8.4\% and 4.3\%, respectively. The median interval between the initial surgery and the occurrence of SPLC was 92 months and 31 months for patients with AIS and MIA, respectively. Therefore, those who developed SPLC and need a second operation would experience further loss of functional lung tissue. Supposing the patient has merely undergone a wedge resection for an AIS/MIA nodule in the first operation, the hilar structure was preserved intact, which creates an opportunity for a successful second operation and better life quality. In the study by Yotsukura et al.\textsuperscript{38}, 56.3\% of the patients underwent lobectomy, and 17.6\% underwent segmentectomy; whereas in the study by Li et al.\textsuperscript{39}, 36.8\% underwent lobectomy and 0.8\% underwent segmentectomy. If it were not for the deeper location of non-peripheral tumors otherwise treatable by wedge resection, lobectomy or segmentectomy would have been deemed as less lung-sparing for this group of patients.

Surgical strategy based on inaccurate radiological criteria may not accord with individualized approach. Fortunately, wedge resection is enough for IAC within 2.0 cm and CTR \leq 0.25 and did not cause undertreatment in JCOG0804. Nevertheless, approximately 50\% of the patients in JCOG1211 were AIS/MIA, and indistinguishable segmentectomy according to the radiological criteria would cause overtreatment. Hence, the predictive ability of the radiological classification adopted from the study JCOG0201 needs to be improved. According to the multi-center
prospective clinical trial Eastern Cooperative Thoracic Oncology Projects 1008 (ECTOP-1008) by Ye et al. 44, for GGO-featured LUAD no more than 1.0 cm or over 2.0 cm, radiologic criteria showed good performance in identifying pathologic invasion, with diagnostic accuracy being 96.0% and 93.1%, respectively. However, for tumor sizes between 1.0 to 2.0 cm, the diagnostic accuracy was 70.7% and intraoperative FS should be resorted to. In the era of precision medicine 45, tailored disease prevention and treatment should be considered. We should find a way to predict with high validity. Compared with the CTR criteria of JCOG studies, the above-mentioned anatomic lung resection guided by an intraoperative FS showed its superiority (Fig. 2). It is essential to understand the indications for limited resection, make evidence-based decisions, and balance undertreatment and overtreatment to endeavor lung-sparing individualized approach.

CALGB140503 and JCOG0802

As for small NSCLC tumors (≤ 2.0 cm) with more solid components (CTR > 0.50), studies CALGB140503 46,47 and JCOG0802 48 were launched to compare the efficacy of sublobectomy with lobectomy in 2007 and 2009 respectively (Fig. 2). Both studies reported non-inferiority of segmentectomy. Although different studies may not be compared, the survival difference between CALGB140503 and JCOG0802 should not simply be attributed to “racial disparity”, other factors including age, gender, cancer-driver gene mutation status, tobacco smoking history, etc., should be considered and balanced beforehand. The CALGB140503 reported that wedge resection (59.1%) and segmentectomy (37.9%) were non-inferior to lobectomy concerning 5-year OS (80.3% vs. 78.9%), 5-year disease-free survival (DFS) (63.6% vs. 64.1%), locoregional or distant recurrence, with the escort of intraoperative FS confirmation of NSCLC and negative LN status. Although the total relapse pattern in the JCOG0802 was similar in both groups, the locoregional relapse in the
segmentectomy group occurred more than twice as much as in the lobectomy group (11% vs. 5%), which may be the result of compromised segmentectomy or expanded indications. Thus, segmentectomy with FS confirmed sufficient surgical margin and negative LN biopsy result was suggested as the standard surgical procedure for this range of patients.

Curative Time Window

GGO-featured LUAD represents a special stage in the natural evolution of lung cancer and a unique clinical subtype with distinctive features and prognosis. Zhang et al. found that CT screening-detected lung cancer is present in a significant proportion of young Asian female non-smokers, most of whom with early stage and extremely good prognosis.

However, approximately 20% of pure GGOs and 40% of part-solid GGOs grew or became more solid after 2.4 years or 4.9 years, respectively. The surgical timing for GGO-featured LUAD is critical, as the status quo of overtreatment for this range of patients has attracted worldwide attention. Hereby, to avoid under- or overtreatment, the surgical curative time window is proposed and defined as stages during which the postoperative 5-year RFS or DFS reaches 100%. Patients who underwent surgical resection (mostly wedge resection) within the curative time window could be considered definitively cured.

A more accurate diagnosis will help clinical decision-making. As more than 90% of persistent and slowly growing GGOs turn out to be malignant, those that have an increase in size or the appearance of a solid component need further evaluation. Unfortunately, the natural evolution pace is not even through each stage. In clinical practice, we have observed the progression of
untreated small GGOs that eventually require more invasive treatment (Fig. 3). At the very start, wedge resection is curative enough. However, as time goes by, radical segmentectomy or lobectomy needs to be done if left untreated in time. After all, if a tumor could be removed in the first place when they are controllable, it would help maximize the opportunity to cure and minimize postoperative complications. For those persistent GGOs that remain stable for a long time, their natural evolution may last years or even decades, which offers a long curative time window. To prevent overdiagnosis and overtreatment, the comparison of the natural course of GGO-featured LUAD with the patient’s life expectancy is crucial. To understand the concept of the curative time window, we could think of it this way: if the patient’s life expectancy is shorter than what it takes for his GGOs to progress to the point that this is the reason for the patient’s survival being shortened, surgery may not be recommended. On the contrary, if the patient is likely to outlive the time interval to lung cancer-specific death, suitable surgical treatment within the curative time window is recommended, with no concerns of overdiagnosis or overtreatment. After all, we have evolved to a lung-sparing era.

As for the estimation of the natural evolution of the nodule, it could be obtained from continuous estimation of the traits on CT scans during follow-up. In addition, life expectancy can be estimated by the patient’s age, general health condition, and the regional average lifespan. As life expectancy differs from person to person, we could borrow the experience of insurance companies on how they calculate the remaining lifespan of their clients. Our surgical strategy for pre- and minimally invasive LUAD entails resecting only persistent GGO lesions, which achieved a malignant rate being 92.6%, while the National Lung Screening Trial (NLST) reported a malignant rate of 75.6%.
To this day, based on the shift of the spectrum and deeper understanding of LUAD, the resection strategy for early-stage NSCLC shifted from pneumonectomy, and lobectomy to limited resections. However, studies of high-level evidence are still pending (Fig. 4, Supplementary Table). For large (> 2.0 cm) central tumors, anatomic lobectomy is undoubtedly still the recognized standard surgical approach, and thus will not be elaborated herein. However, given the deeper understanding of small peripheral NSCLC, several prospective clinical studies have been launched to fill in the gaps between unmet needs and a more individualized approach. For NSCLC tumors ≤ 2.0 cm with CTR between 0.25 and 0.50, the retrospective study by Zhang et al. proved and extended its surgical indication for wedge resection. Due to the lack of prospective evidence, the related clinical trial ECTOP-1020 (NCT06102161) is ongoing. For NSCLC tumors ≤ 2.0 cm with CTR between 0.50 and 1.0, study NCT06028412 has been launched to compare segmentectomy with lobectomy. Similarly, for NSCLC tumors greater than 2.0 cm but less than 3.0 cm with CTR ≤ 0.50, segmentectomy could be curative enough, and the related prospective clinical trial ECTOP-1012 is ongoing.

There are still limitations in what we currently know and what is yet to be studied. For example, in the curative time window, we haven’t found the indicators to sort out patients who do not need any treatment. In the aspect of selective lymph node dissection, some patients with large tumor sizes but without lymph node metastasis have not been able to be picked out before surgery. We only know after surgery after doing unnecessary LND for these LN-negative patients. Some patients’ prognoses are good and do not need any treatment after surgery. Some large nodules are
in advantageous segments that are amenable to segmentectomy and obtain enough margin, therefore, lobectomy could be avoided. By combining innovative approaches and tracers for solid nodules, we are also conducting clinical trials including ECTOP-1017, hoping to obtain more information on the tumor and the lymph nodes before surgery. All we do is just try to illuminate the unknown and strive for more individualized treatment.

References


42. Long-term Outcome of Patients with Peripheral Ground Glass Opacity Dominant Lung Cancer After Sublobar Resections: Final Report of JCOG0804/WJOG4507L.


**Figure legends:**

- Figure 1. Summary of the shift of surgical treatment for lung cancer in chronological order.
- Figure 2. Surgical strategy based on radiology or pathology.
- Figure 3. Examples of untreated small GGOs progress as time goes by. A-D, A 65-year-old female with a nodule that enlarged significantly from January 2014 (A) to May 2020 (D). The result of the CT-guided percutaneous lung biopsy showed LUAD. E-I, A GGO nodule that became larger and more solid during five years of follow-up.
- Figure 4. Evolving guidelines for the surgical strategy of NSCLC.
- Table. Pros and cons of existing trials and the key landmark papers.
- Supplementary Table. Highlights of the key recommendations. (*: Tumor center located peripherally (i.e., in the outer third of the lung field) found by CT scan. #: All evaluations for distant disease must be negative. WEG or SEG is performed only after the FS confirmation of the required nodal station nodes are negative and the resection is confirmed by the surgeon to be technically feasible.*)
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<th>Clinical Trials</th>
<th>Pros</th>
<th>Cons</th>
<th>Key References</th>
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| JCOG0201         | - Defined radiological noninvasive peripheral LUAD as: tumor size ≤ 2 cm and CTR ≤ 0.25   · Specificity: 98.7% | - Observational study  
- Failing to meet primary endpoints  
- The definition and cutoff value of radiological non-invasive were obtained from subgroup analysis  
- Based on the third edition of the WHO International Histological Classification of Tumors, without considering lymphovascular invasion or LNM | [32, 33] |
| JCOG0804         | - 5y-RFS: 99.7%  
- 5y-RFS for IAC: 99.1% | - Observational, non-randomized study  
- Subjective criteria, could vary person-by-person  
- Predictive accuracy: 62.2%  
- The good prognosis covered up the fact of low accuracy of the JCOG0201 radiological standard | [41, 42] |
| JCOG1211         | - 5y-RFS: 98%  
- 5y-RFS for IAC: 97% | - 47% (58-11%) of pts could have received WEG, therefore causing extensive procedure  
- Predictive accuracy: 42% | [43] |
| JCOG0802         | - 5y-RFS: SEG (88%) vs. LOB (87.9%) | - Compared to LOB, significantly higher local recurrence rate in SEG (assuming inappropriate indication for SEG, preservation of intersegmental veins, or inadequate resection margin) | [48] |
| CALGB140503      | - 5y-RFS: Sub-LOB (63.6%) vs. LOB (64.1%)  
- Key point: with the escort of FS-confirmed LN status | - Mixed WEG and SEG, which is better is unknown  
- Approximately 60% have undergone WEG | [46, 47] |
| ECTOP-1008       | Diagnostic accuracy:  
- ≤ 1 cm: 96.0%  
- > 2 cm: 93.1% | Low diagnostic accuracy between 1 cm and 2 cm: 70.7% | [44] |
| Intraoperative FS analysis | - Highest accuracy  
- 5-year RFS: 100%  
- Adequate for FS-underestimated IAC (5-year RFS: 100%) | Non-randomized study | [35-37, 39] |

Table. Pros and cons of existing trials and the key landmark papers.
Figure. 1 Summary of the shift of surgical treatment for lung cancer in chronological order.
Figure. 2 Surgical strategy based on radiology or pathology.
Figure. 3 Examples of untreated small GGOs that progress as time goes by.
Figure. 4 Evolving guidelines for the surgical strategy of NSCLC.
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<th>Location</th>
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<td>0.5 &lt; CTR &lt; 1</td>
<td>SEG without compromised procedure</td>
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Supplementary Table. Highlights of the key recommendations.

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