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REVIEW

Optimal delivery of follow-up care following pulmonary lobectomy for lung cancer

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Introduction: The rationale for oncologic surveillance following pulmonary lobectomy is to detect recurrent disease or a second primary lung cancer early enough so that an intervention can increase survival and/or improve quality of life. Therefore, we reviewed literature for international guidelines and reorganized these useful factors associated with non-small-cell lung cancer (NSCLC) recurrence as remedies in postoperative follow-up.

Method: The population of interest for this review was patients who had been treated with complete resection for primary NSCLC and were in follow-up.

Result: Guidelines on follow-up care for NSCLC vary internationally. Because of the production of progressive medical modalities, the current follow-up care should be corrected.

Conclusion: The specific follow-up schedule for computed tomography imaging may be more or less frequent, depending upon risk factors for recurrence. Many different predictors of postoperative recurrence may help to optimize the patient selection for specified surveillance guidelines and personalized adjuvant therapies to prevent possibly occult micrometastases and to get a better outcome.

Keywords: lung cancer, follow-up, surveillance, recurrence

Introduction

Lung cancer is the most commonly diagnosed cancer worldwide, with incidence rates continuing to increase in developing countries.[1] Optimal follow-up care following pulmonary lobectomy for non-small-cell lung cancer (NSCLC) includes close surveillance for early detection of disease recurrence or second primary lung cancer and proper management for recurrence or second primary lung cancer. The majority of deaths in postresectional treatment of NSCLC are related to the development of recurrence.[2,3] Close surveillance is required for survivors of lung cancer who have received definitive therapy but are at risk for recurrence of their disease and for the development of second primary lung cancers.[4,5] There is a paucity of evidence for different follow-up strategies for patients with lung cancer as well as information about their cost effectiveness. International recommendations for follow-up after curative intent treatment for lung cancer are systematically reviewed comparing follow-up regimes in lung cancer.[6] Multiple factors influence survival following disease recurrence. Risk factors of postoperative recurrence and/or metastatic disease in patients with NSCLC may enable us to optimize the patient selection for proper management with better outcome. However, few recent studies integrated the relationship of clinicopathologic variables and recurrence of NSCLC after pulmonary lobectomy in patients into the

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follow-up guiding principle. Therefore, we reviewed literature for international guidelines and reorganized these useful factors associated with NSCLC recurrence as remedies in postoperative follow-up.

Methods

Search strategy

We aimed at identifying all literature related to follow-up of patients with lung cancer. Searches were conducted in September and October 2015. Relevant articles were identified and retrieved from Ovid Medline and PubMed by internet search. The selected articles were staged according to the seventh edition of the American Joint Committee on Cancer adopted in 2009.[7]

Inclusion and exclusion criteria

The population of interest for this review was patients older than 18 years (with no upper age limit) who had been treated with complete resection for primary NSCLC and were in follow-up. All stages of lung cancer were included in the review. In line with previous reviews and published guidance, lung cancer follow-up is defined as care after treatment, which is planned and multifaceted. Primary outcomes included overall survival. Secondary outcomes were time to detection of recurrence or death. Only studies that reported at least one of the primary outcomes were included. Because of limited reported data, cost was not included as a formal outcome measure.

Recurrences in this review included locoregional recurrences and distant metastases. Although randomized controlled trials are widely regarded as the most appropriate design to evaluate efficacy of an intervention, a scoping review identified a paucity of studies using this design. This approach may potentially result in less robust studies being used for the development of evidence but provides the best evidence currently available in this underresearched area.

Results

Guidelines on follow-up care for NSCLC vary internationally and are listed in Table 1. There are five guidelines, including different follow-up frequency, clinical evaluation, and medical modality. Because of the production of progressive medical modalities, the current follow-up care should be corrected. Low-dose computed tomography (LDCT)[8] or minimal-dose computed tomography (MnDCT)[9] without contrast may be a reasonable option over chest X-ray for detection of pulmonary lesions. The surveillance imaging frequency would be 3, 6, 12, 18, and 24 months and then annually after curative-intent therapy. Diagnostic chest CT with contrast plus upper abdomen scan is suggested to detect local recurrence or new primary lung cancer. If the patient is symptomatic, imaging modality specific to the patient's symptoms is recommended.

Table 2 lists the comparison of common clinicopathologic variables for recurrence of NSCLC following pulmonary lobectomy. These predictors included poor differentiation, squamous cell carcinoma (SCC), smoking history, tumor location, lymphovascular space invasion (LVSI), tumor maximum standard uptake value (SUV_{max}), carcinoembryonic antigen (CEA) value, epidermal growth factor receptor (EGFR), and tumor size. The most common risk factor for recurrence of NSCLC following pulmonary lobectomy is poor differentiation.

Table 1 Comparison of international guidelines for follow-up after curative intent treatment for lung cancer

Guidelines	Frequency	Clinical evaluation and medical modality
NCCN[16]	6 months for 2 years, then annually	History, clinical examination, and chest CT scan with/without contrast for first 2 years, then noncontrast-enhanced chest CT scan annually.
International consensus statement[17]	3 months for the first 2 years, then every 6 months up to 5 years	History, clinical examination, and chest X-ray-CT scans and other tests should be performed in case of clinical indication and smoking cessation.
NICE[18]	All patients to be offered an initial specialist follow-up appointment within 6 weeks of completing treatment to discuss ongoing care. Offer regular appointments thereafter, rather than relying on patients requesting appointments when they experience symptoms	Offer protocol-driven follow-up led by a lung cancer clinical nurse specialist as an option for patients with a life expectancy of more than 3 months. Ensure that patients know how to contact the lung cancer clinical nurse specialist involved in their care between their scheduled hospital visits.
ACCP[8]	6 months for 2 years, then annually	History, examination, imaging CT, CXR.
ESMO[19]	6 months for first 2 years, and every 12 months thereafter (for early-stage and locally advanced NSCLC)	History, physical examination, imaging.

Abbreviations: CXR, chest X-ray; NSCLC, non-small-cell lung cancer; CT, computed tomography; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Clinical Excellence; ACCP, American College of Chest Physicians; ESMO, European Society for Medical Oncology.

Table 2 Comparison of common clinicopathologic variables for recurrence of NSCLC following pulmonary lobectomy

References	Risk factors									
	Poor differentiation	SCC	Smoking history	Tumor location	LVSI	Tumor SUV_{max}	CEA value	EGFR	Tumor size	Population staging
Zhang et al[20]	+	−	−	+	+	−	−	−	+	IA
Kuo et al[21]	+	−	−	−	+	−	+	−	+	I
Chen et al[12]	+	−	−	−	+	−	−	−	−	I (pathologic stage)
Chen et al[3]	+	−	−	−	−	−	+	−	−	I (clinical stage)
Park et al[22]	−	−	−	−	−	+	−	−	−	IA
Jiang et al[23]	−	−	−	−	−	−	+	−	−	IA (<1 cm)
Tao et al[24]	−	+	−	−	+	−	−	−	−	IA
Izar et al[25]	−	−	−	−	−	−	−	+	+	IA
Kobayashi et al[26]	+	−	−	−	−	−	−	−	−	IA
Kozu et al[27]	−	−	−	−	−	−	+	−	+	I
Choi et al[28]	+	−	+	−	−	−	−	−	−	I
Cho et al[29]	+	−	−	−	−	−	−	−	−	I
Guo et al[30]	−	−	+	−	−	−	−	−	−	I–III
Nguyen et al[31]	−	−	−	−	−	+	−	−	−	I–III

Abbreviations: SCC, squamous cell carcinoma; LVSI, lymphovascular space invasion; SUV_{max}, maximum standard uptake value; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor.

Table 3 lists the comparison of uncommon risk factors for postoperative recurrence of NSCLC. These factors were total lesion glycolysis (TLG), survivin overexpression, glucosylceramide synthase, fibroblast growth factor 9, expression of Id-1 and VEGF, reactive oxygen species modulator 1 (Romo1) expression, FoxM1, preoperative peripheral lymphocyte count, Ki-67 labeling index, CD66b-positive neutrophil-to-CD8-positive lymphocyte ratio (iNTR), p53R2, preoperative plasma D-dimer, the significance and handling of microscopic invasion of NSCLC into hilar peribronchovascular soft tissue (SHEATH+), and tumor necrosis.

Discussion

The rationale for oncologic surveillance following initial treatment of lung cancer is to detect recurrent disease or a second primary lung cancer early enough so that an intervention

Table 3 Comparison of uncommon risk factors for postoperative recurrence of NSCLC

References	Prognostic factor	Comment
Park et al[22]	TLG	A significant prognostic factor for OS in patients with Stage IA NSCLC
Cho et al[29]	Survivin overexpression	An independent predictor of recurrence and poor disease-free survival in resected NSCLC
He et al[32]		
Zhang et al[33]	Glucosylceramide synthase	Contributes to the development of NSCLC and could be a useful prognostic indicator and chemoresistance predictor for NSCLC patients
Ohgino et al[34]	Fibroblast growth factor 9	A novel unfavorable prognostic indicator and a candidate therapeutic target of NSCLC
Kim et al[35]	Expression of Id-1 and VEGF	A candidate for therapeutic target and a prognostic factor in NSCLC
Lee et al[36]	Romo1 expression	Significantly associated with early recurrence and poor survival in surgically resected NSCLC
Xu et al[37]	FoxM1	An independent risk factor for recurrence of NSCLC
Zhang et al[38]	Preoperative peripheral lymphocyte count	An independent favorable prognostic factor of DFS in patients with NSCLC who underwent lobectomy and lymph node dissection and adjuvant chemotherapy
Yamashita et al[39]	Ki-67 labeling index	A prognostic factor of disease-free survival in NSCLC and the treatment of choice for patients with positive LI may be considered, in addition to adjuvant chemotherapy, or lobectomy
Ilie et al[40]	iNTR	Independent prognostic factor for a high rate of disease recurrence and poor OS in patients with resectable NSCLC
Hsu et al[41]	p53R2	A biomarker for overall survival and an indicator for tumor recurrence
Wang et al[42]	Preoperative plasma D-dimer	A poor prognostic factor within 1 year after the surgery in NSCLC
Sakai et al[43]	SHEATH+	Simply associated with central occurrence and advanced TNM stages
Park et al[44]	Tumor necrosis	An adverse risk factor for survival and recurrence in patients with Stage IA NSCLC. Thus, close observation and individualized adjuvant therapy might be helpful for patients with Stage IA NSCLC with tumor necrosis.

Abbreviations: TLG, total lesion glycolysis; OS, overall survival; NSCLC, non-small-cell lung cancer; Romo1, reactive oxygen species modulator 1; DFS, disease-free survival; iNTR, CD66b-positive neutrophil-to-CD8-positive lymphocyte ratio; SHEATH+, the significance and handling of microscopic invasion of NSCLC into hilar peribronchovascular soft tissue; LI, labeling index; TNM, tumor-node-metastasis.

can increase survival and/or improve quality of life. Even with completely resected early stage lung cancer, recurrence rates are high. Unfortunately, the majority of recurrences present at distant sites and have a poor prognosis, but a small proportion of patients do present with localized and potentially salvageable relapses. The majority of locoregional and distant recurrences occur within the first 2 years.[10] When planning posttreatment surveillance, care should be taken to limit the number of CT scans if possible, particularly in younger individuals. There are no randomized trials comparing different surveillance strategies in patients with NSCLC. The evidence from observational studies and a systematic review of the literature[6] does not establish a clear-cut benefit for aggressive surveillance following treatment with curative intent. There are no data comparing full-dose, diagnostic, contrast-enhanced CT with LDCT and MnDCT. Given the desire to minimize radiation exposure and the potential for continued screening for many years, some physicians use LDCT even in the initial period after NSCLC treatment. In view of new imaging modalities, such as LDCT[8] and MnDCT scan,[9] the radiation injury for patients with NSCLC after surgery could be enormously decreased. Patients who have had lung cancer are also at increased risk of a second primary, particularly of the lung, and may benefit from early detection of a second primary as well as from detection of a local recurrence. Therefore, annual LDCT[8] may be continued beyond 3 years for patients who have no evidence of disease since these individuals are at risk for a second primary lung cancer as well as for recurrence. The specific follow-up schedule for CT imaging may be more or less frequent, depending upon risk factors for recurrence.

In a series of 1,073 patients who underwent a complete resection, recurrent NSCLC was identified in 445 patients (41%).[11] The median time to recurrence following surgery was 11.5 months, and the median survival following recurrence was 8.1 months. Multivariate analysis identified several factors that predicted shorter survival following recurrence. These included poor performance status, disease-free interval of 1 year or less, prior use of neoadjuvant chemotherapy or adjuvant radiotherapy, and distant metastases (as opposed to intrathoracic recurrence alone). In our previous research,[3] 261 patients with clinical Stage I NSCLC after complete resection and dissection of mediastinal lymph nodes were reviewed. Only 17 patients (6.5%) had locoregional recurrences, and 20 (7.66%) of the same population had distant metastases. We found that tumor differentiation and serum CEA were independent predicators of postoperative relapse for clinical Stage I NSCLC after surgical resection. Risk factors of postoperative recurrence in patients with NSCLC may enable us to optimize the patient selection for postoperative adjuvant therapies to prevent possibly occult micrometastases.[12] One of the purposes of this study is to get together all possible predictors of postoperative recurrences in patients with NSCLC (Tables 2 and 3). However, what kind of surveillance duration and follow-up modalities could really benefit these selected patients with specific risk factors of postoperative recurrence of NSCLC? Prospective multi-institutional studies or randomized clinical trials are mandatory to further validate the predictors of recurrence in NSCLC and specially designated surveillance guidelines for these selected patients.

Currently there is no established indication for targeted agents as adjuvant therapies outside of a clinical trial setting for patients with resectable NSCLC, and its use in this setting is controversial. There is suggestive evidence that EGFR mutation-positive early stage patients have a superior recurrence-free survival with erlotinib, particularly patients with resected Stage IIIA N2 disease.[13,14] Whether this translates to an improvement in overall survival or merely delays recurrence is unknown. Randomized clinical trials are evaluating the role of EGFR- or ALK-targeted therapies in the adjuvant setting for molecularly selected patients. The rapid progression of molecular biology and genetic technique provide clinicians with tools to diagnose and treat diseases more precisely. EGFR mutation test can sieve out suitable cases, who are sensitive to EGFR TKIs, from patients with recurrences of NSCLC after adjuvant erlotinib therapy.[13,14] Besides, immune checkpoint inhibitors, which unleash a patient's own T-cells to kill tumors, are revolutionizing cancer treatment. Rizvi et al[15] used whole-exome sequencing of NSCLC samples treated with pembrolizumab, an antibody targeting programmed cell death-1 (PD-1) to unravel the genomic determinants of response to this therapy. The results suggest that the genomic landscape of lung cancers shapes response to anti-PD-1 therapy.

Conclusion

Annual LDCT, which causes less radiation harm, may be continued beyond 3 years for patients who have no evidence of disease since these individuals are at risk for a second primary lung cancer as well as for recurrence. The specific follow-up schedule for CT imaging may be more or less frequent, depending upon risk factors for recurrence. Many different predictors of postoperative recurrence in patients with NSCLC may enable us to optimize the patient selection for specified surveillance guidelines and design personalized

adjuvant therapies to prevent possibly occult micrometastases and to get better outcome.

Disclosure

There was no substantial direct or indirect commercial financial incentive associated with publishing this article. The authors report no conflicts of interest in this work.

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