Lung cancer surgery for older patients: a narrative review

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: T Murakawa; (III) Provision of study materials or patients: H Hino; (IV) Collection and assembly of data: H Hino; (V) Data analysis and interpretation: H Hino; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background and Objective: Lung cancer is a common cause of cancer-related mortality globally. Progressively aging populations and an increasing incidence of lung cancer among them are concerning in developed and developing countries. However, no established treatment strategy for early-stage lung cancer, especially non-small cell lung cancer, in patients aged ≥75 years exists. Therefore, this review aimed to evaluate recent impactful publications regarding surgery and radiation therapy for older patients with early-staged lung cancer and provide a desirable prospective strategy for their treatment.

Methods: We searched English publications regarding lung cancer surgery for older patients, particularly octogenarians, and radiation therapy reported between 1997 and 2022 using PubMed. We stratified these studies by outcomes of surgery and radiation therapy, postoperative quality of life and sarcopenia, and psychological changes.

Key Content and Findings: The outcomes of octogenarian lung cancer surgery were mostly acceptable and reasonable and better than expected in older generations than in younger generations. Surgeons selected optimal healthy older patients with lung cancer for surgery and provided other treatment modalities, such as radiation therapy or good supportive care, for surgically ineligible patients despite some cases requiring further consideration. The type of surgery, including lobectomy, segmentectomy, or wedge resection, and whether lymph node dissection was performed or not impacted the survival of older patients according to recent publications. In addition to cancer curability, postoperative quality of life of older patients was non-inferior to that of younger patients based on a limited cohort study, although the follow-up duration was not long. Additionally, the impact of sarcopenia, frailty, and postoperative psychological changes, such as delirium, on postoperative outcomes of older patients was investigated. Finally, we highlighted the significance of collaboration among medical staff and development of optimal objective criteria for surgical eligibility and procedure selection for patients with multiple comorbidities, which will contribute to better outcomes.

Conclusions: We have summarized the latest studies regarding lung cancer (mostly surgical) treatment among older patients and provided a useful base for the development of an optimal treatment strategy. Additionally, we have contributed a future perspective for selecting the optimal treatment modality for older patients with lung cancer.

Keywords: Lung cancer surgery; octogenarians/older patients; overall survival; radiotherapy; quality of life

Received: 29 November 2022; Accepted: 04 August 2023; Published online: 22 August 2023.

doi: 10.21037/ccts-22-12

View this article at: https://dx.doi.org/10.21037/ccts-22-12

Introduction

Lung cancer is a leading cause of cancer-related mortality globally, and the number of older patients afflicted by it is increasing (1,2). In Japan, the number of older lung cancer patients aged 80 or above undergoing surgery has increased up to 1.5 times compared to 10 years ago (from 2,273/26,092, 8.7% in 2007 to 5,779/44,140, 13.1% in 2017) (3,4). According to past publications, the results of select overall outcomes of surgery for older lung cancer patients, despite being poorer than those of younger generations, were still acceptable; the postoperative morbidity rate was 20–28%, while mortality rate 2.3–8% (5,6). Previous review articles have summarized the outcomes of lung cancer surgery in older patients; however, they merely stated the surgical results based on several older studies (7-9). Surgical resection is the most effective therapeutic intervention for lung cancer; however, it is associated with a relatively high risk of morbidity and mortality, especially for older patients, which is a major concern for surgeons. Furthermore, there are no definitive criteria for surgical indication, appropriate procedures of limited resection or radical lobectomy, and postoperative follow-ups in our daily clinical practice, which also contribute to this complex issue faced by the older generation but not the younger ones. Recent publications demonstrated that the postoperative complication rate and long-term survival of older patients who underwent lung cancer surgery were reasonable (7,9); therefore, active surgical treatment is considered desirable. However, objective optimal surgical indications and procedures and outpatient follow-ups based on appropriate risk management, especially for borderline patients with multiple comorbidities, are unclear. Thus, this presents a major knowledge gap in lung cancer surgery for older patients.

This review aimed to analyze recent impactful publications regarding lung cancer surgery and radiation therapy in older patients and provide a desirable prospective for treating older patients with lung cancer. This article is presented in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-22-12/rc).

Methods

We reviewed English publications regarding human clinical studies from January 1997 to October 2022 on lung cancer in older patients, which were searched for in the MEDLINE database of PubMed. The search was conducted on 31 October 2022, and the following search terms were used: "octogenarian lung cancer surgery" and "non-small cell lung cancer and "elderly lung cancer surgery", and nonagenarian lung cancer surgery", or "radiation therapy for lung cancer" or "sarcopenia and frailty of elderly lung cancer", or "octogenarian lung cancer" or "quality of life after lung cancer surgery", and "delirium after lung cancer surgery", all associated with lung cancer or gerontological issues in older patients. We restricted the included articles to those on octogenarian lung cancer surgery, and excluded case reports, studies with a sample size under 50, and systematic reviews. Two authors, primarily Haruaki Hino, selected these publications, and the final selection was made after consensus by both. The detailed search results for this review article are demonstrated in *Table 1* and *Table 2*.

Definition of older patient with non-small cell lung cancer

The aging of populations is a serious socioeconomic problem worldwide. The World Health Organization recently defined individuals aged ≥65 years as older people; those aged 65–74 and ≥75 years are called early- and late-stage older patients, respectively (10). Moreover, Japan has one of the most rapidly aging populations globally, and the Japan Gerontological Society recently advocated that the new definition for "old" should be categorized into "pre-old" patients aged 65–74 years, "true-old" patients aged ≥75 years, and "oldest-old" or "super-old" patients aged ≥90 years (11). In clinical practice, individuals aged ≥75 years are widely accepted as older patients based on evidence that recent clinical trials or studies regarding surgeries or chemotherapy with newly developed drugs mostly include patients aged ≤75 years. Regarding the surgical indications for older patients, the North American and European guidelines commonly state that "age" alone is not a contraindication for lung cancer surgery (12-14). Indications for lung cancer surgery in older patients with multiple comorbidities are controversial, and no definitive surgical indications have been established. In recent clinical practice, surgeons assess patients based on their performance status, cardiopulmonary function, comorbidity, cognitive function, and social background to decide on performing surgery, whether it should be radical or limited, and if lymph node dissection is required or not. In the 1990s, outcomes of lung cancer surgery in older patients, mostly defined as septuagenarians, were reported (15-17). Subsequently, the age of patients with non-small cell lung cancer has been increasing with approximately half of them aged ≥70 years (1,4). Although there were

Table 1 The search strategy summary

Items	Specification
Date of search	31 October 2022
Databases and other sources searched	The MEDLINE database of PubMed
Search terms used	"octogenarian lung cancer surgery" and "non-small cell lung cancer and "elderly lung cancer surgery", and nonagenarian lung cancer surgery", or "radiation therapy for lung cancer" or "sarcopenia and frailty of elderly lung cancer", or "octogenarian lung cancer" or "quality of life after lung cancer surgery", and "delirium after lung cancer surgery"
Timeframe	From January 1997 to October 2022
Inclusion and exclusion criteria	Inclusion: the above-mentioned method and publications searched by those key words. Exclusion: case reports, studies with a sample size under 50, systematic reviews, and non-English literature
Selection process	Two authors, primarily Haruaki Hino, selected the publications, and the final selection was made after consensus by both
Any additional considerations, if applicable	Rare case series with a sample size under 50 were included; additionally, studies on surgery for nonagenarian, comparison between octogenarian and younger patients, lymph node dissection for octogenarian, radiotherapy for octogenarian, and quality of life after surgery among older patient were considered

Table 2 Summary of search strategy for older lung cancer surgery

No.	Searches	Results
1	Octogenarian lung cancer surgery	159
2	Octogenarian non-small cell lung cancer	106
3	Elderly lung cancer surgery	47,466
4	1 and 2 and 3	37
5	Nonagenarian lung cancer surgery	13
6	3 and 7	3
7	Octogenarian lung cancer	189
8	Radiation therapy for lung cancer	39,594
9	7 and 8	12
10	Quality of life after lung cancer surgery	1,368
11	1 and 2 and 3 and 10	8
12	Sarcopenia and frailty of elderly lung cancer	12
13	3 and 12	25
14	Delirium after lung cancer surgery	27
15	3 and 14	6

reports that included lung cancer patients aged 70 or older, the outcomes of these patients did not differ much from that of the entire cohort; thus, it did not describe the true characteristics of older lung cancer patients. To investigate and explore clinically accurate features of older lung cancer patients undergoing surgery and discuss the outcomes unique to these patients, surgeons raised the age cutoff value in the definition of older patients to 80 or above. Accordingly, studies of lung cancer surgery in older patients emphasized on older generations, considering individuals aged ≥80 years as an accurate starting point. Thereafter, surgeons considered that older patients with lung cancer aged ≥80 years had comparatively higher surgical risks than other patients who fell under the category of "old" patient. Therefore, we reviewed various studies regarding non-small cell lung cancer surgery in older patients, particularly octogenarians, and other treatment modalities using the latest issues and provided a useful base for future treatment.

Postoperative complications and mortality among older patients with lung cancer

In a study by Oxnard *et al.* (18), among octogenarians with all clinical stages of lung cancer, surgery was performed for 17.1% (19/111) of them, a number smaller than the number of surgeries performed for younger patients. Surgeons should acknowledge that only a few candidates are eligible for surgery among all patients with non-small cell lung cancer, especially octogenarians. Reports of non-small cell lung cancer clinical or pathological stage I to III among octogenarians undergoing surgery increased from the early 2000s. The reported surgical results from prospective and retrospective cohorts with >50 patients each between 1997 and 2021 are summarized in *Table 3* (19-37).

Table 3 Surgical morbidity, mortality, and risk factors for complications in octogenarians with lung cancer

Year	Author	Study design	Sample size	Stage	Morbidity (%)	Mortality (%)	Risk factors for complications
1997	Pagni S (19)	Single-center retrospective	54	c-stage I–IIIA	42.0	3.7	N/A
2004	Brock MV (20)	Single-center retrospective	68	c-stage I–IV	88.0	8.8	N/A
2004	Port JL (21)	Single-center retrospective	61	c-stage I–IIIA	38.0	1.6	N/A
2005	McVay CL (22)	Single-center retrospective	159	c-stage I	18.0	1.8	N/A
2006	Dominguez-Ventura A (23)	Single-center retrospective	379	p-stage I–IV	48.0	6.3	Congestive heart failure, myocardial infarction
2006	Allen MS (24)	Multicenter prospective	70	c-stage I–III	49.0	2.9	N/A
2007	Ikeda N (25)	Single-center retrospective	73	c-stage I–IV	37.0	4.1	N/A
2007	Brokx HA (26)	Multicenter retrospective	124	c-stage I–IV	ND	4.0	N/A
2008	Mun M (27)	Single-center retrospective	55	c-stage I	25.6	3.6	N/A
2009	Okami J (28)	Multicenter retrospective	367	c-stage I	8.4	1.4	Comorbidity, mediastinal lymph node dissection
2011	Fanucchi O (29)	Single-center retrospective	82	c-stage I–II	30.4	2.4	N/A
2011	Berry MF (30)	Single-center retrospective	193	p-stage I–IV	46.0	3.6	Extent of resection, thoracotomy, impaired lung function
2015	Hino H (31)	Single-center retrospective	94	c-stage I–IIIA	27.0	1.1	N/A
2015	Matsuoka K (32)	Single-center retrospective	174	c-stage I–II	24.3	1.15	Low body mass index
2018	Detillon DDEMA (33)	Nationwide retrospective	168	N/A	42.3	6.0	Low respiratory function, low ASA, coronary artery bypass graft, COPD, thoracotomy, radical resection
2018	Hino H (34)	Multicenter retrospective	337	c-stage I–IIIA	35.3	1.8	Male sex, operation time
2018	Saji H (35)	Nationwide prospective	895	c-stage I–IIIA	34	1.6	Male sex, CGA7, low albumin level, low VC%, SCS
2021	Saftic I (36)	Single-center retrospective	257	c-stage I–III	43.6	3.11	COPD
2021	Bongiolatti S (37)	Multicenter retrospective	329	c-stage I–III	45.2	1.2	Age ≥80 years, male sex, CCI >4, Performance status >1, FEV1% <60, DLCO <60%

N/A, not analyzed; ND, not determined; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CGA, comprehensive geriatric assessment; VC, vital capacity; SCS, Simplified Comorbidity Score; CCI, Charlson Comorbidity Index; FEV1%, forced expiratory volume in one second; DLCO, diffusing capacity of the lung for carbon monoxide.

Table 4 Surgical outcomes of octogenarians with lung cancer compared with that of younger patients

Year	Author	Sample size	Stage	Comparison (years) [n]	Principal findings
2013	Srisomboon C (38)	24	All stages	75–79 [70]	Morbidity, mortality, and OS were almost equivalent to those of younger populations
2018	Detillon DDEMA (33)	168	All stages	60–69 [1,031], 70–79 [934]	Mortality was higher; however, morbidity was equivalent to that of younger populations
2018	Hong S (39)	34	c-stage I	50–79 [457]	Morbidity, mortality, and survival (OS and RFS) were equivalent to those of the younger population
2020	Nakao M (40)	70	cN0	70–79 [205]	Morbidity, mortality, and survival (OS and CSS) were equivalent to those of younger populations

OS, overall survival; RFS, recurrence-free survival; CSS, cancer-specific survival.

Table 5 Surgical outcome comparison between early and late octogenarian patients with lung cancer

Author	Total sample size (n)	80–84 years (n)	≥85 years (n)	Principal findings
Smelt J (41)	94	76	18	Morbidity and mortality were equivalent
Iijima Y (42)	76	64	12	Age ≥85 years and cigarette smoking were poor prognostic factors for OS and RFS
Ichinokawa H (43)	394	320	74	Morbidity, mortality, and survival were equivalent

OS, overall survival; RFS, recurrence-free survival.

The mean/median (range) morbidity and mortality rates were 37.9/37.5% (8.4–88.0%) and 3.2/2.9% (1.1–8.8%), respectively, which demonstrated that most studies reported acceptable outcomes that were improving with time. In detail, preoperative co-morbidity was present in 33.5–91.0% of patients, and patients who underwent radical lobectomy, bi-lobectomy or pneumonectomy presented a rate as high as 66.8–92.9%, demonstrating that even older lung cancer patients with several comorbidities were able to undergo radical surgery with acceptable outcomes (23,26,28,32-35). Concurrently, the number of older patients with lung cancer who do not have severe co-morbidity has been increasing. In contrast, in patients with multiple comorbidities and a poor performance status, limited surgery is likely to be indicated to reduce the risk of postoperative complications resulting from the optimal selection by the surgeon. However, surgical indications and procedures for patients with multiple comorbidities, lower pulmonary function, or poor performance status are difficult to ascertain because no definitive indications and guidelines have been established for these scenarios. Recent publications have reported the differences in the surgical outcomes between octogenarians and younger generations. Detillon *et al.* reported a significantly higher mortality following octogenarian lung cancer surgery; however, the morbidity was similar to that of younger generations based on a Dutch nationwide database (33). In contrast, according to Japanese and Korean single institutional analyses, the morbidity and mortality of octogenarians after lung cancer surgery were almost equivalent to those of septuagenarians using propensity score matching (*Table 4*) (33,38-40). On comparing early and late octogenarians undergoing surgery, postoperative morbidity and survival were similar between the two groups (*Table 5*) (41-43). Moreover, some studies pertained to nonagenarian lung cancer surgery (*Table 6*). Limited case studies in Japan showed no postoperative mortality (44,45), however, Yang *et al.* demonstrated that the 90-day mortality rate was as high as approximately 10% using an American database (46); to clarify the short-term outcomes, we may use database scoring system produced by the Surgeon of Thoracic Society database [2012–2014] from the United States of America, the European Society of Thoracic Surgeons database from Europa or National Clinical Database from Japan to predict the postoperative morbidity and mortality with high accuracy (47-49). When using systems that take into account factors such as multiple comorbidities, performance status and respiratory function, not only surgeons but also lung cancer patients and their

Table 6 Surgical outcomes of nonagenarian patients with lung cancer

Author	Sample size	Principal findings
Iwata T (44)	2	No surgical mortality after omitting mediastinal lymph node dissection
Miyazaki T (45)	5	No surgical mortality with acceptable survival (median 3.4 years)
Yang CJ (46)	266	Of 7,205 nonagenarians, 266 (3.7%) underwent surgery with a 90-day mortality rate of 12.4%

family could achieve a consensus and arrive at a desirable postoperative outcome, especially in the case of marginal high-risk older lung cancer patients. In summary, the short-term outcomes of lung cancer surgery in older patients were considered almost acceptable even when compared that of a younger population aged under 60 years. These results are most likely the reflection of the evidence that surgeons decided an indication and procedure based on performance status and cardiopulmonary ability as well as using surgical risk score and their experience to make an optimal selection. For cases where the surgical indications are unclear, a clear set of criteria or guidelines are required for improved clinical practice and treatment outcomes.

Prognostic factors for surgical octogenarian patients

Long-term survival outcomes after lung cancer surgery in octogenarians are listed in *Table 7* (19-21,25-29,31,32,34,36,50). Postoperative mean and median (range) 5-year overall survival (OS) rates of patients, including those with stages I–IV cancers, were 45.5% and 43.0% (24.0–66.1%), respectively, which were deemed acceptable outcomes, although they were negatively impacted by age, comorbidity, and conditions with minimal adjuvant therapy. Regarding prognostic factors for long-term survival in the octogenarian cohort, higher age, male sex, multiple comorbidities, lower respiratory function, extent of resection, and higher tumor stages were reported as predictors of poor survival. The other reported poor prognostic factors are non-adenocarcinoma histology, lower Glasgow Prognostic Score, and resection status (R1 and R2), which are comprehensive and common prognostic variables. Although the surgical indications, procedures, and patient nationalities varied among the studies, the long-term survivals and prognostic factors detected were similar; this demonstrates that surgeons use similar criteria to determine surgical eligibility and select procedures targeting octogenarians with lung cancer.

Regarding the etiology of death, lung and non-lung cancer-associated mortality is another specific issue among older patients with lung cancer. These patients have a short life expectancy and a high non-cancer-related mortality rate, which affect their survival irrespective of the cancer stage. Hino *et al.* performed a competing risk analysis for lung- and non-cancer-related deaths and reported that limited resection and higher pathological stages were significantly associated with higher cancer-specific death; conversely, male sex, coronary artery disease, and higher pathological stages were significantly associated with higher non-cancer-specific death (51). Therefore, they suggested that surgical procedures should be carefully selected due to their impact on the etiology of death. Mimae *et al.* demonstrated that wedge resection reduced other causes of lung cancer-associated death in patients with non-small cell lung cancer aged ≥80 years compared to that in younger patients (52); they suggested that wedge resection might be a better alternative to radical surgery in terms of etiology of death among octogenarians with non-small cell lung cancer. Since these were small cohort studies analyzing the postoperative etiology of death among octogenarian patients with lung cancer, the results of a prospective ongoing study in Japan (JCOG2109), evaluating wedge resection *vs.* segmentectomy for small-sized peripherally located lung cancer in octogenarian, is expected to provide an appropriate insight on the efficient treatment strategy in the near future. In summary, long-term survival of octogenarians was shorter than that of younger populations because of short life expectancy and increased non-cancer-related deaths. However, oncological survival between both groups was similar; therefore, surgery for eligible octogenarian patients with lung cancer can improve cancer curability despite several age-related issues.

Surgical procedures: lobectomy vs. limited/sublobar resection

Regarding optimal surgical procedures for lung cancer, the extents of lung resection and lymph node dissection are controversial as prognostic factors. Ginsberg *et al.* demonstrated that lobectomy provided increased survival compared with limited surgery in 1995, which has been propagated until now (53). Recently, a Japanese nationwide

Table 7 Postoperative survival and prognostic factors for octogenarians with lung cancer undergoing surgery

Year	Author	Study design	Sample size	Stage	5-year overall survival (%)	Prognostic factors
1997	Pagni S (19)	Single-center retrospective	54	c-stage I–IIIA	43.0	N/A
2004	Brock MV (20)	Single-center retrospective	68	c-stage I–IV	34.0	Advanced tumor stage, lower ASA physical status, low FEV1
2004	Port JL (21)	Single-center retrospective	61	c-stage I–IIIA	38.0	N/A
2007	Ikeda N (25)	Single-center retrospective	73	c-stage I–IV	57.4	N/A
2007	Dominguez-Ventura A (50)	Single-center retrospective	294	p-stage I–IV	34.0	Extent of resection, p-stage
2007	Brokx HA (26)	Multicenter retrospective	124	c-stage I–IV	24.0	N/A
2008	Mun M (27)	Single-center retrospective	55	c-stage I	65.9	N/A
2009	Okami J (28)	Multicenter retrospective	367	c-stage I	55.7	N/A
2011	Fanucchi O (29)	Single-center retrospective	82	c-stage I–II	27.0	Male sex, ACE-27
2015	Hino H (31)	Single-center retrospective	94	c-stage I-IIIA	57.5	Male sex, non-adenocarcinoma
2015	Matsuoka K (32)	Single-center retrospective	174	c-stage I–II	48.3	N/A
2018	Hino H (34)	Multicenter retrospective	337	c-stage I–IIIA	66.1	Male sex, CCI, GPS, p-stage
2021	Saftic I (36)	Single-center retrospective	257	c-stage I–III	40.8	p-stage, resection status

N/A, not analyzed; ASA, American Society of Anesthesiologists; FEV1, forced expiratory volume in one second; ACE-27, Adult Co-Morbidity Evaluation-27; CCI, Charlson Comorbidity Index; GPS, Glasgow Prognostic Score.

prospective study (JCOG0802/WJOG4607L) showed that segmentectomy had an equivalent overall survival to lobectomy limited to clinical stage IA, tumor diameter ≤2 cm, and consolidation-to-tumor ratio >0.5 (54). A similar study for clinical stage IA lung cancer with radiographic tumor sizes <1, 1–1.5, and >1.5–2.0 cm is currently being performed in North America (CALGB/Alliance 140503) (55). Another Japanese nationwide retrospective study validated the non-inferiority of segmentectomy to lobectomy for clinical tumor stages of cT1b or less (56). In terms of indications for an older cohort, limited surgery (segmentectomy or wedge resection) is favored for individuals with multiple comorbidities, low respiratory function, and poor performance status. The study results comparing radical lobectomy and limited surgery were controversial (*Table 8*) (31,57-64). In Japanese cohort studies of patients aged ≥80 years with lung cancer, wedge resection had an acceptable impact on morbidity, and similar survival was seen, especially for small-size lung cancer, with whole tumor sizes ≤2 cm and consolidation-to-tumor ratio >0.5 (60,61). Other similar studies of lung cancer in patients aged ≥75 years reported equivalent short-term results and long-term survival between sublobar resection and lobectomy (57-59,62,64). Regarding patient age and procedure, survival after lobectomy was superior to that after limited surgery at ages ≤71 years; however, this survival difference diminished in patients aged >71 years according to an American Database surveillance (65). This study, although two decades old, showed that a radical surgical procedure did not necessarily affect the prolonged survival of older patients. In contrast, an American nationwide database study for patients with lung cancer aged 80 or above

Table 8 Comparison of surgical outcomes between lobectomy and sublobar resection among older patients with lung cancer

Year	Author	Sample size	Age (years)	Stage	Procedure [n]	Principal findings
2018	Tsutani Y (57)	205	≥75	c-stage I	Lobectomy [106], segmentectomy [56], wedge resection [43]	Sublobar resection had equivalent morbidity and survival to lobectomy
2018	Yutaka Y (58)	232	≥75	c-stage I	Lobectomy [156], segmentectomy [50], wedge resection [26]	Sublobar resection had equivalent morbidity and survival to lobectomy
2018	Hino H (31)	337	≥80	c-stage I–IIIA	Lobectomy [237], Segmentectomy [28], wedge resection [66]	Sublobar resection was not a significant predictor of OS
2019	Zhang Z (59)	1579	≥75	c-stage I	Lobectomy [1,164], Segmentectomy [106], Wedge resection [309]	Sublobar resection was associated with significantly better perioperative outcomes
2020	Mimae T (60)	58	≥80	c-stage IA	Lobectomy [21], Segmentectomy [9], wedge resection [28]	Wedge resection had equivalent survival (OS and RFS) to lobectomy and segmentectomy
2021	Mimae T (61)	156	≥80	c-stage IA	Lobectomy + segmentectomy [90], wedge resection [66]	Wedge resection had equivalent morbidity, mortality, and long-term survival to radical surgery
2021	Zhang X (62)	3345	≥75	p-stage I	Lobectomy [2,415], Segmentectomy [194], Wedge resection [736]	Wedge resection should be considered for tumor size ≤1 cm
2022	Chan EY (63)	25362	≥80	p-stage I	Lobectomy [14,594], Segmentectomy [1,192], Wedge resection [5,178]	Lobectomy was superior to segmentectomy and wedge resection in those aged ≥80 years
2021	Lin YJ (64)	258	≥75	p-stage I	Lobectomy [84], Segmentectomy [46], Wedge resection [128]	Sublobar resection had equivalent morbidity and survival to lobectomy

OS, overall survival; RFS, recurrence-free survival.

demonstrated that survival after lobectomy was superior to that after sublobar resection; the 5-year OS rates were 48.5% *vs.* 41.1% (P<0.001) in the unmatched cohort and 51.2% *vs.* 41.1% (P<0.001) in the matched cohort, respectively (63). However, in this cohort, the median tumor size for sublobar resection was 19 mm, which was relatively larger than that considered for lobectomy (25 mm). Moreover, among sublobar resections, including segmentectomy and wedge resection, the number of wedge resections was approximately 5 times higher than that of segmentectomies (n=5,178 *vs.* 1,192, respectively), which may explain the inferiority of sublobar resection compared to lobectomy.

Two retrospective studies of lung cancer among individuals aged ≥75 years and octogenarians, respectively, described sublobar resection as a prognostic factor (34,58). They reported that segmentectomy and wedge resection were not significant risk factors for OS compared with lobectomy. In fact, preoperative comorbidity might have a greater impact on OS. Then, as a procedure, sublobar resection might be more successful in reducing non-cancer mortality, especially in the older cohort. Taken together, sublobar resection for small-sized tumors of approximately ≤2 cm in diameter located in the peripheral lung field seems to be a feasible procedure for older patients with comorbidities or cardiopulmonary dysfunction who are ineligible for lobectomy. In clinical practice, a surgical procedure balancing the oncological impact and severity of comorbidity and cardiopulmonary function on a case-by-case basis for older patients is necessary.

Significance of lymph node dissection for octogenarians with lung cancer

Several studies and trials have described the significance of lymph node dissection during lung cancer surgery (66-70). Overall, its role has been to aid in tumor staging and provide survival benefits for all generations. In that regard, a few Japanese studies have elaborated the significance of lymph node dissection for older patients (*Table 9*) (28,71,72).

Table 9 Lymph node dissection for octogenarians with lung cancer undergoing lung resection

Year	Author	Sample size	Stage	Principal findings
2009	Okami J (28)	367	c-stage I	MLND and preoperative comorbidity were associated with postoperative complications
2009	Chida M (71)	48	All stages	MLND was associated with cardiac complications and worse survival than non-MLND
2022	Nakao M (72)	622	c-stage I–IIIA	Survival of patients after HLND was equivalent to that of patients who underwent MLND for early-stage NSCLC

MLND, mediastinal lymph node dissection; HLND, hilar lymph node dissection; NSCLC, non-small cell lung cancer.

Okami *et al.* reported that mediastinal lymph node dissection and preoperative comorbidity were significantly associated with postoperative complications in octogenarians who underwent surgery for clinical stage I lung cancer (28). Additionally, Chida *et al.* showed that mediastinal lymph node dissection for a small cohort (n=48) of octogenarian patients with lung cancer increased the incidence of postoperative cardiac complications and increased mortality (71). Recently, Nakao *et al.* demonstrated that omitting mediastinal lymph node dissection for octogenarian patients with early-stage lung cancer had an equivalent impact to that of performing mediastinal lymph node dissection on overall and disease-free survivals using data from a Japanese nationwide database and propensity score matching (72). Originally, lymph node dissection was used to obtain an accurate lymph node staging and subsequently administer postoperative adjuvant therapy. However, among patients aged ≥75 years, adjuvant chemotherapy is generally not indicated due to aged-related organ damage, making lymph node dissection unnecessary. Therefore, mediastinal lymph node dissection for small-sized lung cancer in patients aged ≥75 years with multiple comorbidities and impaired cardiopulmonary function may be omitted. However, large cohort studies further clarifying the significance of mediastinal lymph node dissection for older patients are required to confirm this.

Radiation as an alternative therapy for octogenarian patients with non-small cell lung cancer

Non-surgical procedures, such as radiation therapy, are employed for older patients with early-stage lung cancer who are ineligible for surgery. According to the guidelines published 3rd edition of American College of Chest Physicians, stereotactic body radiation therapy (SBRT), as an alternative treatment modality to surgery, is introduced as a definitive treatment and provides the best supportive care (73). Some studies regarding radiation therapy for octogenarians with lung cancer reported decreased morbidity with acceptable survival in these patients; however, the survival was poorer than that obtained with surgery (*Table 10*) (74-85). Recently, SBRT or other high-energy therapies, including carbon-ion radiotherapy and proton beam therapy, are increasingly indicated to control small-sized lung cancers in inoperable patients and have lower morbidity and mortality than surgery. Furthermore, Karnofsky Performance Status, inoperability, solid nodule, tumor size, higher C-reactive protein level, and tumor histology were reported as significant prognostic factors for lung cancer patients who underwent radiotherapy (77,79,83). According to several studies, the median OS of octogenarian lung cancer patient who underwent SBRT *vs.* surgery was reported as 3.5 *vs.* 5.6 years (76), 35.5 *vs.* 56.4 months (79), and 53 *vs.* 70 months (83) and 5-year OS as 27% *vs.* 50% (81), respectively, demonstrating that the survival of patients undergoing SBRT was considerably lower than that of patients undergoing surgery even after propensity score matching. We considered that majority of the patients treated with SBRT were inoperable and had a poor performance status, cardiopulmonary function, and nutritional status. Therefore, SBRT can be used for octogenarians with lung cancer and comorbidities to reduce treatment-associated adverse events despite its lower survival impact than surgery. A large cohort study is expected to clarify the optimal indications for SBRT or surgery, particularly for older patients.

Postoperative quality of life (QOL) among older patients with lung cancer

QOL after lung resection is an important postoperative consideration for older patients with lung cancer and has been reported in several studies, including review articles (86,87) targeting septuagenarians and octogenarians (*Table 11*) (88-95). Burfeind *et al.*, using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire to estimate the QOL, including

Table 10 Radiotherapy for octogenarians with lung cancer

Year	Author	Sample size	Stage	Procedure	Principal findings
2010	van der Voort van Zyp NC (74)	38	c-stage I	SBRT	2-year OS rate was 44% without grade 4 or 5 treatment-related toxicity
2014	Sandhu AP (75)	24	c-stage I	SBRT	2-year OS and local control rates were 74 and 77% without grade ≥3 treatment-related toxicities
2014	Cannon NA (76)	30	c-stage I–IV	SBRT	1- and 2-year OS rates were 69 and 36%, respectively, with no grade 4 and 5 toxicities
2016	Koyi H (77)	48	c-stage I–IV	SBRT	Median OS rate was 3.5 years compared with that of surgery (5.6 years)
2017	Cassidy RJ (78)	58	c-stage I	SBRT	Higher KPS was a significant prognostic factor for RFS and OS
2018	Lee K (79)	422	N.D.	SBRT	Median OS rates of SBRT and surgery groups were 35.5% and 56.4%, respectively
2020	Bei Y (80)	153	c-stage I–II	SBRT	3-year OS rate was 65.3%. Tumor size, CRP level, histology, and performance status were prognostic factors
2020	de Ruiter JC (81)	895	p-stage I, II	SBRT	5-year OS rate was 27% for SBRT compared with that for surgery (50%)
2021	Watanabe K (82)	64	c-stage 0–IIA	SBRT	5-year OS rate was 47.5%. Inoperability and solid nodule were prognostic factors
2021	Razi SS (83)	286	c-stage I	SBRT	Lobectomy had superior survival compared with SBRT using propensity score matching
2021	Hayashi K (84)	32	c-stage IIA–IIIB	CIRT	The 2-year PFS and OS were 46.7% and 68.0%, respectively, with no grade ≥ IV toxicities
2022	Nakamura M (85)	42	c-stage I–II	PBT	3-year OS and PFS rates were 79.8 and 73.9%, respectively. Survival was not inferior to that of younger populations

SBRT, stereotactic body radiation therapy; RFS, relapse-free survival; OS, overall survival; CRP, C-reactive protein; KPS, Karnofsky Performance Status; PFS, progression-free survival; CIRT, carbon-ion radiotherapy; PBT, proton-beam therapy.

physical, emotional, and social aspects, reported that the QOL of patients aged ≥70 years 3 months postoperatively was poor; however, after 6 months, their QOL was similar to younger patients (88). An Italian nationwide study reported that octogenarians with lung cancer who underwent thoracoscopic lobectomy had poor scores of EuroQol 5-dimensions 5-levels at discharge; however, the QOL was equivalent to that of younger patient after 1 month, demonstrating a slower recovery period in older patients (94). However, Schulte *et al.* revealed that patients aged ≥70 years failed to make a complete recovery compared with younger patients (92). These conclusions varied between the studies possibly because of their limitations, including selection bias and variations of measurement procedures, QOL criteria, and postsurgical intervals. Moreover, these study cohorts were small and the observational periods were as short as 1 year; therefore, long-term sequelae were not evaluated. Future research regarding variations in QOL stratified by treatment modalities, including surgery *vs.* radiation therapy and lobectomy *vs.* sublobar resection, with multi-institutional large cohorts is required. Additionally, studying QOL changes over long follow-up periods (at least once a year) is desirable.

Sarcopenia, frailty, and postoperative delirium

With the growing number of older patients with lung cancer, not only surgical approach or procedure but also gerontological changes of physical senescence, including sarcopenia, frailty, and psychological alterations, such as cognitive decline and perioperative delirium, which are specific to older patients, should be considered. According to past publications, patients with lung cancer along with frailty and decreased muscle volume and strength consequently experienced a deteriorated overall and oncological survival (*Table 12*) (96-120). In detail, declining psoas muscle area (98,103,106,107,111,113,116,118,119), pectoralis muscle area (99,102,115,120), or skeletal muscle

Table 11 QOL after lung cancer surgery among septuagenarians and octogenarians

Year	Author	Age (years)	Total sample size	Stage	Principal findings
Septuagenarian					
2008	Burfeind WR Jr (88)	<70 *vs.* ≥70	422	c-stage I–II	Postoperative QOL of the older cohort was reduced at 3 months; however, QOL after 6 months was similar between the younger and older cohorts
2009	Ferguson MK (89)	<70 *vs.* ≥70	124	c-stage I–II	QOL after recovery from lung resection was similar between younger and older patients
2009	Salati M (90)	<70 *vs.* ≥70	218	ND	SF36 domains did not differ between younger and older patients
2009	Balduyck B (91)	70–79	60	stage I–III	Lobectomy provides a more favorable evolution of QOL subscales than pneumonectomy
2010	Schulute T (92)	<70 *vs.* ≥70	131	ND	Older patients failed to make a complete recovery
Octogenarian					
2011	Vicidomini ND (93)	<80 *vs.* ≥80	42	ND	The thoracotomy group had a significant reduction in the dyspnea index, FEV1, and DLCO
2021	Bongiolatti S (94)	<80 *vs.* ≥80	7,023	c-stage I–III	EuroQoL5D of octogenarians was worse at discharge; however, the score was similar to that of younger populations after 1 month
2022	Asemota N (95)	<80 *vs.* ≥80	106	p-stage I–III	Postoperative QOL of octogenarians remains similar to that of younger patients

QOL, quality of life; SF-36, 36-item Short Form Health Survey; ND, not described; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity of the lung for carbon monoxide; EuroQoL5D, EuroQol 5-dimensional questionnaire.

volume (96,97,100,101,104,105,108-110,112,114,117), preoperatively measured on computed tomography, had a great negative impact, recently intensively researched, on the survival of patients with lung cancer undergoing surgery. Furthermore, preoperative body weight and albumin levels in blood samples (Geriatric Nutrition Risk Index), reflecting sarcopenia, demonstrated accurate prediction for overall and oncological survival, especially for older patients with lung cancer (121). Hence, the preoperative approaches to intervene those gerontological change might possibly improve survival of older patients with non-small cell lung cancer. Subsequent prospective studies of nutritional interventions preventing sarcopenia and frailty might be necessary to clarify whether improving the nutritional condition would prolong life expectancy, especially for older patients with non-small cell lung cancer. Moreover, perioperative psychological changes, particularly delirium, are important to consider in older patients. Delirium is a well-known postoperative complication as per the European guidelines (122). However, accurate etiology and effective prevention and treatment measures following lung cancer surgery in older patients are unclear. Recent studies reported that the postoperative delirium rate was 3.3–6.7%; cerebrovascular disease history, squamous cell carcinoma, depression, current smoking status, and age ≥75 years were significant risk factors for postoperative delirium; and patients who developed delirium had significantly decreased OS (123,124). Additionally, ramelteon or dexmedetomidine reportedly reduced delirium after lung cancer surgery (125-127). However, these study cohorts were small; therefore, these findings should be carefully considered, and psychiatry changes should be carefully monitored during lung cancer surgery.

Future perspective

With a progressively aging society, all these surgical and gerontological issues for non-small lung cancer treatment should be completely investigated and collaborated by medical staff, including surgeons and internal medicine physicians; co-medical staff, including physical therapists, medical social workers, and nutritionists; and the older

Table 12 Sarcopenia preoperatively measured for lung cancer patient undergoing surgery

Year	Author	Total sample size	Measured score/object
2016	Suzuki Y (96)	90	The sum of cross-sectional areas of skeletal muscles in the region of the third lumbar vertebra (L3)
2017	Tsukioka T (97)	215	The cross-section area of muscle at the third lumbar vertebra level
2017	Hervochon R (98)	161	Left psoas areas measured by CT scan at the L3 level
2017	Kinsey CM (99)	252	Pectoralis muscle area measured objectively on chest CT
2018	Kim EY (100)	272	Cross-sectional area of muscle at the third lumbar vertebra
2018	Takamori S (101)	101	Normalized skeletal muscle area at the 12th thoracic vertebra level
2018	Miller JA (102)	299	Cross-sectional area of the erector spinae muscles and pectoralis muscles
2019	Kawaguchi Y (103)	173	Total psoas muscle area at L3 level
2019	Nagata M (104)	468	The 6-month postoperative change in skeletal muscle mass index
2019	Sun C (105)	314	The truncal muscle index at the first lumbar vertebral level
2020	Shinohara S (106)	391	Psoas muscle volume
2020	Shinohara S (107)	391	The cross-sectional area of the psoas muscle at the third lumbar vertebra level
2020	Takamori S (108)	204	The skeletal muscle area at the 12th thoracic vertebra level
2021	Choi H (109)	440	The abdominal total fat volume at the waist and the skeletal muscle area
2021	Çınar HU (110)	120	The thoracic muscle mass
2021	Kawaguchi Y (111)	256	The total psoas muscle area
2021	Troschel FM (112)	367	Muscle cross-sectional area on CT at thoracic vertebral levels T8, T10, and T12
2021	Miura A (113)	259	Psoas muscle mass index
2021	Tanaka S (114)	587	Paraspinous muscles at the level of the 12th thoracic vertebra and preoperative 6MWD
2021	Karapınar K (115)	161	The psoas major muscle, the pectoralis major and minor muscles
2021	Daffrè E (116)	238	Cross-sectional total psoas area, cross-sectional total muscle area, and total parietal muscle area
2021	Kim EY (117)	272	Single cross-sectional area of the skeletal muscle at the 3rd lumbar vertebra (L3) level
2021	Takahashi Y (118)	315	The lowest quartile of psoas muscle area on the 3rd vertebra
2022	Yamada Y (119)	645	Psoas muscle volume
2022	Sun C (120)	341	Pectoralis muscle index

CT, computed tomography, 6MWD, 6-min walk distance.

patients themselves. Based on objective data from many previous and ongoing studies, a desirable decision-making process involving the surgeon as well as patients and their families will promote a favorable outcome in the future.

Limitations and strengths

This study has some limitations. Almost all publications selected for this review were retrospective study series, and the research intervals were >20 years due to the small number of investigations. The studies comprising an older cohort were inevitably observational, and the indications for surgery or radiation were not consistent among the studies. Moreover, newly developed immune checkpoint inhibitors have been recently used for patients with lung cancer after recurrence. As for the strengths of the study, patient outcomes across the studies were mostly consistent, and some common variables, such as prognostic factors, were detected regardless of different countries. Overall, data regarding numerous older patients with non-small cell lung cancer who underwent radical surgery or radiation therapy were collected, allowing a reasonably robust analysis and formulation of future perspectives.

Conclusions

Surgical outcomes of older patients with lung cancer are mostly acceptable. On this basis, we can properly select an operable patient and perform an optimal procedure mainly on a case-by-case basis according to the prior experience of the surgeon. In case of high risk, we may possibly utilize a database risk scoring system in consideration for operative indication and informed consent to a patient. We should clarify the optimal objective selection criteria for surgical indications and procedures in detail, especially for borderline surgical candidates, which will contribute to a favorable outcome. We should also consider an indication of SBRT for older patients with multiple comorbidities, who are unlikely to be eligible for surgery, in order to minimize the risk of perioperative complications. Additionally, the postoperative QOL after lung cancer surgery in older patients seemed to be almost equivalent and demonstrate a relatively slow recovery compared with those of the younger population, according to past publications. Therefore, we should cautiously follow up in older lung cancer patients, especially those with frailty or sarcopenia, in the outpatient clinic. Finally, we should focus on an impact of sarcopenia and frailty of older patient which affect postoperative outcomes especially long-term survival. Then, we might take into consideration for intervention on perioperative nutritional therapy, based on a result of ongoing investigation.

Acknowledgments

We are very grateful to *Editage* for their English proofreading services.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://ccts.amegroups.com/article/view/10.21037/ccts-22-12/rc

Peer Review File: Available at https://ccts.amegroups.com/article/view/10.21037/ccts-22-12/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://ccts.amegroups.com/article/view/10.21037/ccts-22-12/coif). TM serves as an unpaid editorial board member of *Current Challenges in Thoracic Surgery* from November 2021 to October 2023. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/ccts-22-12
Cite this article as: Hino H, Murakawa T. Lung cancer surgery for older patients: a narrative review. Curr Chall Thorac Surg 2023;5:46.