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Surgical treatment of non-small-cell lung cancer in octogenarians

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Abstract

Reluctance to recommend lung cancer surgery for octogenarians is partly based on the expectation that the rate of complications and mortality is higher in this group of patients, and on the impression that the life expectancy of an octogenarian with lung cancer is limited by death from natural causes. Moreover, the belief that radiation therapy and observation yield similar results to surgery in early-stage disease have influenced low resection rates in this population. Nevertheless, advances in surgical techniques, anaesthesia and postoperative care have made surgical lung resection a safer procedure than it was in the past. Judging from the more recent findings, surgery should not be withheld because of postoperative mortality, but suboptimal or palliative treatment may be necessary in patients with poor physical or mental function. To enable informed decision-making, both patients and clinicians need information on the risks of surgical treatment. In this review, available information from the literature was collected in an effort to understand the real benefit of surgical treatment in octogenarians with non-small-cell lung cancer, and to determine what should be done or avoided during the selection course.

Keywords: Lung cancer • Octogenarian • Surgery • Mortality • Survival • Complications

INTRODUCTION

The incidence of non-small-cell lung cancer (NSCLC) in octogenarians is increasing in Western countries. This disease represents the second leading cause of cancer death in this age group, and it is also responsible for a substantial increment in morbidity and health-care costs [1]. Several studies [2, 3] have suggested that age *per se* should not be considered a risk factor for surgical mortality and morbidity in lung cancer patients and access to surgical treatment should not be denied only on the basis of age. Indeed, advanced age may represent an indicator of several factors such as comorbidity or poor physical performance, which in turn can increase surgical risk and dramatically reduce life expectancy [4]. The management of these patients requires an understanding of the predictable changes in pulmonary physiology occurring with surgery and anaesthesia as well as a knowledge of the factors associated with the development of postsurgical complications. The surgical procedure causes reduction of lung capacity and diaphragm dysfunction, and impairs gas exchange and cough and mucociliary clearance, leading to the development of micro-atelectasis and postoperative hypoxaemia [5]. These modifications are exacerbated in chronic obstructive pulmonary disease [6], as well as in older patients [7], survivors of recent myocardial infarction [8], in cases of starvation [9] and smoking patients [10]. Moreover, the octogenarian patients submitted to lung resection procedures developed severe and frequent postoperative complications, so these patients are frequently submitted to preoperative risk evaluation [11]. Advances in surgical and anaesthetic techniques, combined with a detailed preoperative and sophisticated perioperative assessment, have contributed to an increasing number of octogenarians undergoing a successful surgical treatment of NSCLC.

RATIONALE

Life expectancy represents an important component in surgical decision-making, alongside disease parameters and patient choice. Indeed, the issue of life expectancy can make the difference between patients receiving treatment and being denied it. The justification for major cancer operations in octogenarian patients depends on several factors [12, 13]. First, the life expectancy of the subjects must exceed their projected survival if the neoplasm is not treated or is addressed by non-operative modalities. Second, the operative mortality rate for the group should be sufficiently low that it does not negate or substantially blunt the long-term benefit. The third issue, quality of life, is of paramount concern to elderly people and must not be sacrificed for limited added longevity. A fourth concern is sensible resource utilization, an inescapable issue in the current era of cost containment. Finally, and especially relevant in lung cancer, is the need to define the boundaries of operative treatment in the older age group with respect to tumour stage and extent of resection.

RISK FACTORS

Octogenarians present frequently with several coexistent comorbid conditions [14]. In fact, previous studies have shown that

>80% of octogenarians have at least one associated disease and >50% of octogenarians have two or more adverse prognostic comorbidities at the time of lung cancer diagnosis. [15]. Furthermore, comorbidity has been correlated with survival [16] and with postoperative complications [17]. In consideration of the strong relationship between number of comorbid conditions and advanced age, comorbidity may explain the increased mortality risk in octogenarians documented by several studies and confound the association between age and surgical complications. In fact, some authors consider advanced age as a risk factor for mortality and perioperative complications [18, 19], while others disagree with it [20, 21]. Despite early suggestions of an increased risk of pulmonary complications with advanced age, this is not an independent risk factor for pulmonary complications. The healthy status of a patient, mainly cardiorespiratory, seems to be much more important than age [6, 20].

Preoperative risk assessment and evaluation of lung function facilitate the selection of elderly patients who are suitable candidates for pulmonary resection. A detailed assessment based on history, symptoms and signs of chronic lung or heart disease, as well as chest X-ray, electrocardiogram, arterial blood gas analysis, pulmonary function test and biochemical and haematological panel can help in screening potential surgical patients. Preoperative appraisal of pulmonary function factors has been comprehensively studied to forecast morbidity and mortality after pulmonary resection. Many different values have been found to be predictive of pulmonary complications and mortality in patients undergoing lung resection. For example, forced expiratory volume in 1 s (FEV1), forced vital capacity, diffusion capacity of lung for carbon monoxide and postoperative predicted data have all been studied [22]. In the multivariate analysis, patients with percentage-predicted FEV1 <60 were found to experience significantly higher rates of postoperative complications when compared with patients whose percentage-predicted FEV1 was 80 or greater. Moreover, patients with severe chronic obstructive pulmonary disease (COPD) are six times more likely to have a major postoperative complication [23]. Elective surgery should be deferred in patients who are symptomatic, have poor exercise capacity or have acute exacerbation. A partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) of >45 mmHg often occurs in persons with severe COPD and indicates a high risk, although it is not necessarily prohibitive for surgery [24]. However, hypoxaemia was associated with cardiac complications, principally the occurrence of arrhythmias. Anaemic patients had more respiratory and infectious complications, probably due to nutritional deficiencies not identified during the preoperative evaluation. In fact, malnutrition is a risk of morbidity and mortality in critical-care and surgical patients [25], and perioperative blood transfusion was associated with increased postoperative complications [26].

Several scoring systems include associated comorbidities for quantifying surgical risk in lung cancer patients. Harpole *et al*. [27] included American Society of Anesthesiologists (ASA) physical status in their multi-institutional outcome study of major pulmonary resections. Patients with a preoperative ASA status of 4 had a risk of death more than six times than that of those with an ASA status of 2 [28]. Boffa *et al*. [29] analysed the risk factors for patients with a lobectomy for lung cancer using the Society of Thoracic Surgeons General Thoracic Surgery Database. They indicated age, ASA score, male sex, Zubrod score, insulin-dependent diabetes, renal dysfunction, induction therapy, percentage-predicted FEV1 and smoking as risk factors. In France, a thoracic surgery scoring system for in-hospital mortality (Thoracoscore) was developed using data obtained from >15 000 patients who were enrolled in a nationally representative thoracic surgery database. Mortality risk factors included in the model were patient age, sex, dyspnoea score, ASA score, performance status, priority of surgery, diagnosis, procedure class and comorbid disease [30]. The model was subsequently validated on 1675 patients from the USA, where a similar accuracy was noted [31]. Pneumonectomy, Zubrod score and ASA class had the highest impact on short-term outcome.

In conclusion, the decisions on surgical indications, the method and the risk quantification for the selected surgical method should be evaluated separately. Functional data may therefore be relatively less important for determining the surgical indications and the optimal treatment method in comparison with comorbidity risk assessment.

SURGERY AND PATIENT SELECTION

In the past, age >80 years was considered a relative contraindication to pulmonary resection, prompting some to advocate non-operative management or a sublobar resection in this age group [32]. However, advances in preoperative and postoperative care and in surgical technique have encouraged many to offer surgical resection to the elderly population. In fact, during the last two decades, numerous studies (Table 1) involving lung resections in the octogenarian have dismissed older accounts of prohibitively high mortality rates, and have suggested that lobectomies, in particular, are safe and effective.

In fact, evidence-based guidelines recommend that patients with lung cancer should not be denied resection on the grounds of age alone [33]. Treatment decisions for a patient with cancer are based on the performance status and stage of cancer. To predict surgical risk, cardiopulmonary function is assessed preoperatively [34, 35]; however, the surgical options are still restricted for elderly patients, who frequently present with multiple diseases.

The extent of pulmonary resection may influence outcomes in octogenarians [36]. The role of sublobar pulmonary resections remains a controversial area for both elderly and nonelderly patients with early-stage lung cancer, though some evidence is emerging, particularly for octogenarians [37, 38]. Okami *et al*. [39] found no difference in 5-year survival in octogenarians who underwent lobectomy compared with limited resection. However, in a study from the University of Pittsburgh [40], lobectomy was compared with segmentectomy for patients with Stage I NSCLC and segmentectomy was associated with reduced mortality (7.8 vs 2.8%) and improved 3-year survival in a subgroup of 99 octogenarians. So, modified procedures such as wedge resection or segmentectomy are usually recommended in high-risk patients. However, extended segmentectomy for low-risk patients might strike a balance between curability and a low rate of complications. Although specific evidence is lacking, limited surgeries may have a role in octogenarians with limited survival, or possibly for patients with small, peripherally located tumours, who are at significant risk of postoperative complications.

More-extensive surgeries require careful evaluation of the risks and benefits. In octogenarians, pneumonectomy, particularly right sided, is strongly associated with an increased risk of complications as compared with standard lobectomy or limited resection [41, 42]. Mizushima *et al*. [43] reported that operative

Table 1: Surgical series in patients older than 80 years with non-small-cell lung cancer

Reported	Author	No. of years (dates)	No. of patients	Male (%)	Mean age (years)	Preoperative comorbidity (%)	Stage I (%)	MLN evaluation (%)	Lobectomies (%)	Sublobar resections (%)	Pneumonectomy (%)	Complications (%)	Operative mortality (%)	5-year survival (%)
2012	Personal data	5 (2007–11)	57	70.2	82.2	38.6	51.1	57.8	61.4	15.8	8.8	33.3	1.8	–
2011	Fanucchi *et al.* [38]	9 (2001–09)	82	76.8	81.1	23.0	52.5	20.7	76.8	22.0	0	30.4	2.4	36.0
2009	Okami *et al.* [39]	1 (1999)	367	63.2	82.0	27.8	60.9	34.6	66.8	33.2	0	8.4	1.4	56.1
2009	Chida *et al.* [66]	26 (1981–2006)	48	–	81.7	–	62.5	100	89.5	6.3	4.2	68.8	–	35.0
2008	Suemitsu *et al.* [67]	26 (1981–2006)	146	58.2	82.6	–	74.7	100	54.1	37.6	0.7	–	–	46.8
2008	Mun and Kohno [50]	8 (1999–2006)	55	63.4	82.7	91.0	80.0	–	67.3	30.9	0	25.6	3.6	65.9
2008	Bolukbas *et al.* [68]	6 (1999–2004)	47	–	–	–	38.3	100	66.0	–	4.3	38.2	4.3	41.0
2007	Brokx *et al.* [69]	16 (1989–2004)	124	86.3	82.0	–	64.0	–	70.2	4.8	12.1	–	4.0	24.0
2007	Koizumi *et al.* [70]	20 (1982–2001)	32	75.0	82.0	90.6	68.8	59.4	100	0	0	56.2	12.5	46.6
2007	Hope *et al.* [71]	6 (1999–2004)	20	50.0	82.1	–	50.0	–	60.0	–	15.0	45.0	10	39.0
2006	Dominguez *et al.* [65]	20 (1985–2004)	379	65.4	82.0	33.5	67.1	93.4	63.3	28.3	6.6	48.0	6.3	–
2005	Matsuoka *et al.* [72]	8 (1997–2004)	40	75.0	82.0	17.5	87.5	40.0	60.0	30.0	0	20.0	0	56.9
2005	McVay *et al.* [73]	13 (1992–2004)	159	38.0	83.0	–	100	–	96.0	2.0	2.0	18.0	1.8	–
2004	Brock *et al.* [28]	23 (1980–2002)	68	65.0	82.0	39.7	60.3	80.9	69.0	16.0	1.5	44.0	8.8	34.0
2004	Port *et al.* [53]	14 (1990–2003)	61	41.0	82.0	36.1	44.0	100	75.4	8.2	6.5	38.0	1.6	38.0
2003	Aoki *et al.* [74]	17 (1985–2001)	49	53.1	81.2	69.4	100	44.9	100	0	0	41.0	2.0	44.8
2000	Aoki *et al.* [75]	18 (1981–98)	35	62.9	81.4	28.6	68.6	54.3	71.4	28.6	0	21.0	0	39.8
1999	Hanagiri *et al.* [76]	4 (1992–95)	18	–	–	–	50.0	–	66.7	27.8	0	50.0	0	42.6
1997	Pagni *et al.* [13]	16 (1980–95)	54	48.2	82.0	24.0	76.0	–	79.6	5.6	1.8	42.0	3.7	43.0
1994	Naunheim *et al.* [77]	11 (1981–91)	37	55.0	82.7	–	95.0	–	70.2	15.0	13.5	45.0	16.0	30.0
1994	Osaki *et al.* [62]	18 (1974–91)	33	75.8	82.4	67.0	48.0	–	66.7	15.2	9.1	67.0	21.2	32.3
1989	Shirakusa *et al.* [78]	10 (1978–87)	33	78.8	82.0	45.5	54.5	100	63.6	6.1	9.1	51.0	13.0	55.0

mortality after pneumonectomy was 22.2% in patients ≥70 years and significantly differs from that in patients <70 years (3.2%). In fact, bronchoplasty should be performed whenever possible, even in elderly patients, to avoid pneumonectomy [44].

Video-assisted thoracoscopic surgery (VATS) has become popular in the treatment of lung cancer [45, 46]. This minimally invasive procedure is believed to substantially reduce morbidity and mortality in elderly patients. Nagahiro *et al*. [47] and Yim *et al*. [48] reported that VATS generates less pain and cytokine production, and offers better preservation of pulmonary function in the early postoperative phase. Recently, Cattaneo *et al*. [46] have reported that postoperative complications after pulmonary lobectomy in an elderly patient population occurs with a lower frequency with a minimally invasive VATS approach compared with a traditional, rib-spreading thoracotomy (28 vs 45%). This is an important finding because it is well established that operative morbidity and mortality rates for pulmonary resections rise with advancing patient age [49]. Several other authors [45, 46, 50] have reported the efficacy of VATS, which was demonstrated by the lower incidence of morbidity and mortality, and acceptable 5-year survival rate, in octogenarians.

In conclusion, preoperative risk assessment helps in screening potential surgical patients and facilitates the selection of the right surgery for the right patient. Recently, we retrospectively analysed pulmonary resection in the octogenarian population at our institution (personal data not published), focusing on whether age, comorbidity and surgical strategy which influenced the prognosis of elderly patients with lung cancer, to establish the factors that should be considered in the decision to operate on elderly patients. We also formulated a functional decision-algorithm for the surgical management of octogenarian lung cancer patients (Fig. 1).

OPERATIVE MORBIDITY AND MORTALITY

Postoperative mortality after lung resection in octogenarians ranges from 0 to 21% depending on the type of surgery and selection of patients, with a long-term (5-year) survival ranging from 24 to 66% (Table 1). The major causes of death within 30 days have been pneumonia and cardiac complications [51, 52]. Possible reasons for the low perioperative mortality in some series are strict patient selection, improvements in surgical and anaesthetic technique and attempts to avoid pneumonectomy whenever possible [53]. Pneumonectomy is associated with a high incidence of complications, such as supraventricular tachyarrhythmias and respiratory complications (pneumonia, respiratory failure, empyema), and the rate of occurrence of these adverse events is higher for older than younger patients. In addition, in consideration of the lower cardiac and respiratory reserve consistent with physiological aging (not to mention the higher number of comorbidities), in older adults these complications turn out to be fatal in a higher proportion of cases [54]. Pulmonary complications caused by increased bronchial secretion and difficulty in expectoration directly increase mortality, making the prevention of such complications essential. Wound pain and drainage tubes cause elderly patients to restrict their movement and suppress coughing, increasing the risk of coexisting illness after operation. Pain control is mandatory after thoracotomy, particularly in elderly patients [55]. Postoperative pulmonary care including epidural analgesia, bronchoscopy, early ambulation and physical therapy should be extremely aggressive and early. In addition, patients should be instructed not to smoke and to perform deep respirations before operation. The impact of smoking cessation on perioperative outcome has been a matter of considerable debate [56, 57]. The beneficial effects of smoking cessation, including improvement in ciliary and small airway function and a decrease in sputum production, occur gradually over several weeks. The risk is highest in patients who were smoking within the last 2 months, and patients who had quit smoking for >6 months have a risk similar to those who do not smoke [21]. The ACCP recommends that all patients with lung cancer be counselled regarding smoking cessation [33]. ERS/ESTS guidelines recommend smoking cessation for at least 2–4 weeks before surgery, because this may change perioperative smoking behaviour and decrease the risk of postoperative complications [58]. Pulmonary rehabilitation in the perioperative period has been shown to improve measures of activity tolerance, allowing resection of marginal candidates, and improving functional outcomes after resection [59]. The ERS/ESTS guidelines state that early pre- and postoperative rehabilitation may produce functional benefits in resectable lung cancer patients [58].

Therefore, it should not be a surprise that guidelines recommend that patients with Stage I disease should be considered for surgical treatment regardless of age and underline the need for a careful assessment of comorbid conditions preoperatively [34]. Anyway, not all comorbidities have the same impact on survival and a careful selection of patients, based on the kind of comorbidities (in particular cardiovascular and respiratory diseases), more than their number, can be recommended as part of routine preoperative evaluation [60]. It is unclear whether operative morbidity increases with very advanced age, and there is no convincing evidence that patients of this age with Stage I disease have worse prognosis than younger patients. Unfortunately, there are no reports relating specifically to Stage II and III disease, and several studies have shown that in this age group, pneumonectomy is associated with a higher mortality risk. Therefore, in octogenarians, surgery for Stage II and III disease, pneumonectomy and extended resections should be considered only in exceptional cases.

QUALITY OF LIFE

Patient-centred outcomes are gaining importance in orienting health-care management. The focus of health-care providers and the public is gradually shifting from early postoperative endpoints (such as morbidity and mortality) to long-term outcomes, such as survival, residual function and quality of life (QoL) [61]. For decades, surgeons' attitude in evaluating surgical success has focused mainly on minimizing the risk of postoperative complications and death. Fortunately, in the most recent years, this trend has changed, and there is now a greater attention both to what patients really fear about their surgical experience and to the price they are willing to pay for increasing their chance of cure. Many of them are willing to accept even postoperative cardiopulmonary complications, but less so long-term functional disability [62]. Pompili *et al*. [61] found that a considerable proportion of patients experience a large decline in physical and emotional components of their QoL compared with their preoperative status. Furthermore, compared with the general population, nearly half of the patients displayed a depressed physical and emotional status 3 months after surgery. Patients with better preoperative physical functioning and bodily pain perception

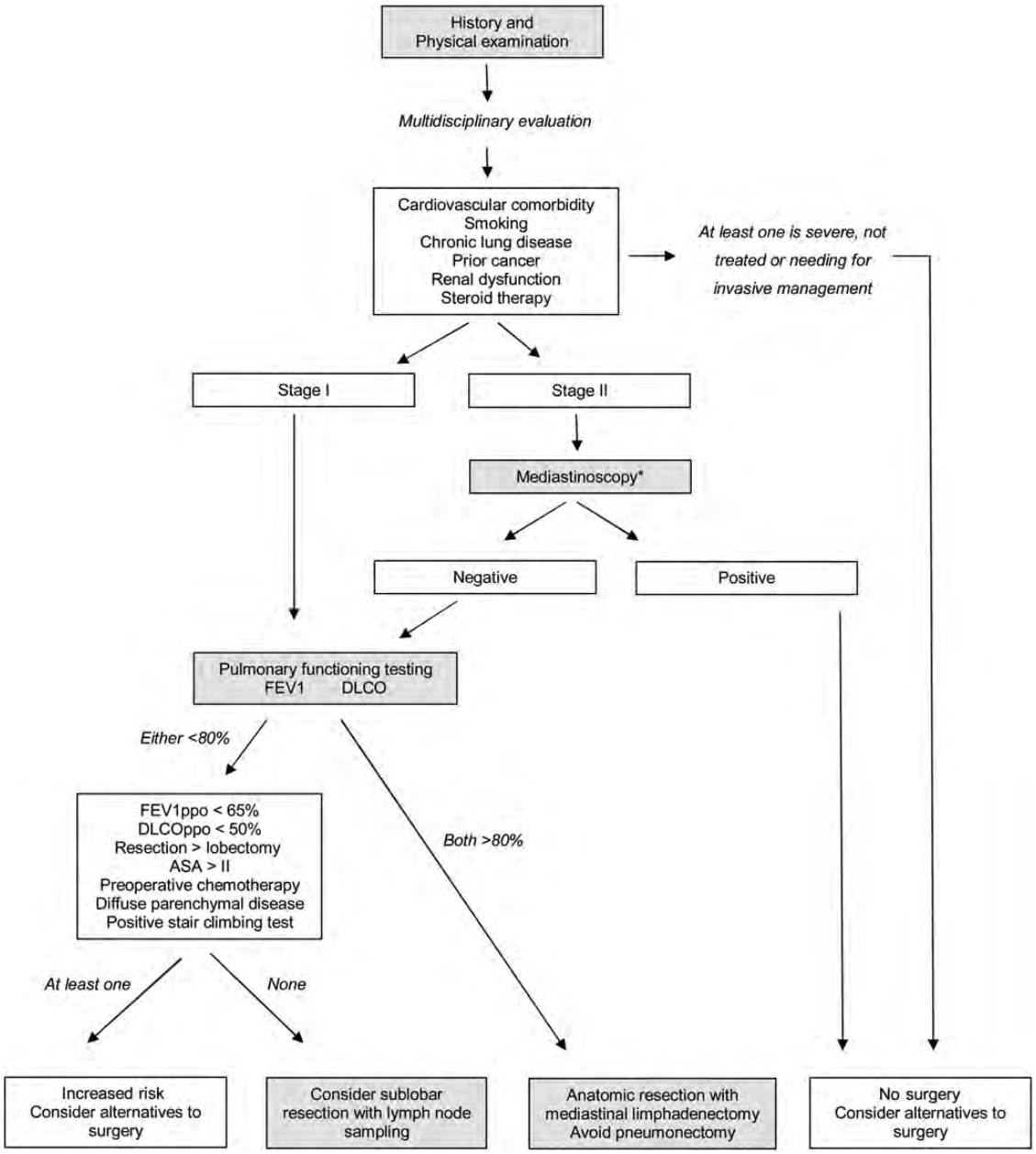

Figure 1: Algorithm for functional evaluation of octogenarian patients being considered for surgical resection of lung cancer—based on recommendations relating to assessment of resectability from evidence-based guidelines for lung cancer proposed by the American College of Chest Physicians. Recommendations were adapted to a specific population and mainly based on physiological and comorbidity conditions. Authors describe how to manage patient selection and how to decide what extension of resection should be performed. The asterix indicates that mediastinoscopy is performed only if lung resection is considered; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide; ppo: predicted postoperative; ASA: American Society of Anaesthesiologists physical status.

(less symptomatic) and those with worse mental health are those at higher risk of experiencing a large physical decline. The risk of perceived emotional decline was found to be greater in patients with lower preoperative FEV1 and higher preoperative social functioning and mental health scores. In general, these findings confirm that patients reporting a better preoperative physical fitness, but with more compromised mental/emotional status, are those more prone to experience severe deterioration of their physical condition. Little is known about the impact of surgical treatment on the quality of life in this age group. When treating patients whose life expectancy is obviously reduced, such as octogenarians, assuring a better quality of life is sometimes more important than trying to ameliorate survival. This should be a subject of future research.

SURVIVAL

Previous series reported 5-year survival rates ranging from 24 to 66% (Table 1). This wide range is likely due to a varying degree of three well-known confounding factors: (i) selection bias; (ii) small sample sizes in each series (range 18–379) and (iii) incompleteness of follow-up.

Even with Stage I disease, however, octogenarians have a lower 5-year survival than published data for younger patients [63, 64]. A lower 5-year survival rate in octogenarians is expected because these patients have a lower life expectancy than younger patients. In the Brock *et al*. [28] cohort, the 5-year survival was also significantly different between Stages Ia and Ib (61 vs 10%). The cumulative evidence suggests that accurate preoperative clinical staging is imperative, and implies a need for more liberal use of sensitive imaging modalities, such as PET scans, to stage octogenarians [13]. When analysing outcomes by extent of resection, the best 5-year survival is achieved in patients undergoing lobectomy or bilobectomy. Sublobar resections are associated with a poor 5-year survival [65]. Here again, a selection bias may be an important confounding factor. In retrospective series, it is likely that limited resections were a surrogate for patients with more severe pre-existing respiratory compromise, leading to less-extensive pulmonary resections. Those undergoing pneumonectomy also have a poorer long-term survival. This likely demonstrates the effect due to both the extent of disease requiring a pneumonectomy for complete resection and the limited ability of these elderly patients to withstand, over the long term, the loss of pulmonary function involved in a pneumonectomy.

CONCLUSION

In conclusion, octogenarians should not be denied surgery solely due to age because properly selected ≥80-year olds with NSCLC can be resected safely with acceptable long-term survival. When surgeons have to take the controversial decision of whether to offer resection to octogenarians, they should base their choice first on the stage of the disease, and then on an accurate assessment of the general clinical conditions, rather than on pulmonary function alone. Surgery offers the best chance of cure for older patients with early stages lung cancer, and mortality rates have reached acceptable levels. Based on the need of a multidisciplinary assessment to identify comorbidities and operative risk, a close collaboration among pneumologists, radiologists, oncologists, thoracic surgeons, anaesthesiologists, cardiologists, geriatric specialists and physical therapists is highly recommended. A concise and standardized preoperative evaluation can provide a suitable and safe postoperative prediction of complications in patients submitted to lung resection, and patients with COPD, hypoxaemic, older, anaemic patients, and in need of pneumonectomy must be classified as high-risk for developing postoperative complications.

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eComment. The role of thoracic surgery in octogenarians with non-small cell lung cancer

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We have read with interest the paper by Guerra *et al.* [1] reviewing the most recent literature on surgical treatment of non-small cell lung cancer (NSCLC) in octogenarians.

Nowadays, this is a notable topic since life expectancy is increasing. In a recent study of the UK population, it has been shown that the greatest population increasing is amongst those aged 85 and over; in 2013 the number is estimated to reach 2.5 million (4% of all population). Moreover, octogenarians are more often considered for lung resection because the number of those who have a diagnosis of lung cancer is growing (from 7.5% to 17% of new diagnoses) [2]. In evaluating the role of thoracic surgery in octogenarians, it must be underlined that also in this group of patients, lung resection is the best chance of cure, especially in early stages. However, published data report that 30% of elderly patients are excluded from surgery, in contrast to 8% of younger patients — and this is often due only to chronological age [3]. The main reason is the belief that age per se is a risk factor for perioperative morbidity and mortality. Other important factors opposing surgery are the shorter life-expectancy and worse postoperative quality of life in the elderly. We would like to focus on two relevant indications emerging from Authors' paper.

The first one is that age per se is not related to an increasing of morbidity and mortality and the surgical risk is related only to comorbidities and poor physical performance. It must be considered that octogenarians have at least one associated disease in 80% of cases, and two or more severe comorbidities in 50%. This means that treatment decision must be tailored on a case by case basis and based on associated diseases and performance status evaluation, independent of age. Focusing on pulmonary function, the Authors reported that this was not a significant predictive factor for complications. On the contrary, Berry *et al.*, in a recent paper, reported that worsening pulmonary function was the only preoperative variable independently predicting complications in octogenarians [4].

The second topic is the kind of resection. Many authors have found no differences in 3- and 5-year survival in octogenarians who underwent lobectomy compared with wedge resection and reported a lower mortality in the latter group. Furthermore, in 2008, Igai *et al.* showed that VATS reduced morbidity and mortality in elderly patients [5]. Therefore, the chance to adopt a mini-invasive approach and to perform a reduced lung resection could further expand the list of surgical indications in this group of patients.

Conflict of interest: none declared.

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