Original Paper

Indications and methods of surgical treatment of solitary pulmonary nodule

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SUMMARY

PURPOSE: The diagnosis and treatment of solitary pulmonary nodule (SPN) is a common but complex clinical problem, for which the investigation of the role of thoracic surgery comprised the purpose of the present study. **METHODS:** By computerized literature search we tried to answer three questions: a) when is surgical resection (diagnostic or therapeutic) of SPN is indicated? b) what type of surgical resection is required {lobectomy or limited (sublobar) lung resection such as wedge resection or anatomic segmentectomy} for malignant SPN? and c) by what method (VATS or open thoracotomy) should be performed biopsy-resection of SPN? **RESULTS:** We noted that the increased probability for malignancy of a SPN as reflected by the existing imaging methods and the failure to set histological diagnosis with modern invasive but non-surgical methods are the main indications for thoracic surgical intervention (diagnostic or therapeutic). About whether lobectomy or sublobar resection is the best surgical treatment approach, we found that although they have comparable survival rates, wedge resection is associated with fewer complications, shorter hospitalization but higher percentages of local recurrences in contrast to anatomic segmentectomy which has similar results to those of lobectomy. As to whether video-assisted thoracic surgery or open thoracotomy is the best diagnostic or therapeutic surgical approach for a SPN, they exhibit comparable results, both diagnostically and therapeutically. **CONCLUSIONS:** More randomized controlled trials are needed for comparing video-assisted thoracic surgery with open thoracotomy and the various types of surgical resection of SPN.
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INTRODUCTION

Solitary pulmonary nodule (SPN) is defined as a comprehensive radiographic lesion with clear boundaries, diameter ≤30 mm, which is completely

surrounded by pulmonary parenchyma, without concomitant atelectasis, mediastinal lymphadenopathy or pleural effusion. This is a fairly common clinical problem, the management of which remains complicated because malignant SPNs must be diagnosed and treated promptly using the possible safer and less invasive method before turning to a surgical approach. An estimated 150,000 SPNs are detected annually in the US, and more frequently in a random chest roentgenogram or a chest computerized tomography (CT). Approximately 30-40% of these are due to malignant neoplasms and the remaining to benign diseases such as specific and non-specific inflammations, vascular malformations, benign tumors, and so forth[1].

Therefore, surgical resection is considered mandatory firstly for malignant SPNs as in early stage non-small cell lung cancer (NSCLC) the 5-year survival rate exceeds 80%, and secondly for benign SPNs because of potential complications such as bleeding, atelectasis, pneumonia or malignant degeneration.

An important factor in SPN management is the 'possibility of malignancy' on the assessment of which have been used methods, such as Bayes analysis and logistic regression. Generally, when the possibility for malignancy is considered 'low' periodical monitoring of the lesion is recommended usually with low dose chest CT. As the probability increases, the necessity to set histological diagnosis or to remove the SPN surgically ensues, moving always from the less to the more invasive diagnostic methods, and when they fail, we turn to surgical diagnosis and treatment methods, the most commonly used of which are: a) video-assisted thoracic surgery (VATS), and b) conventional open thoracotomy.

In this review we tried to answer three questions: a) when is surgical resection (diagnostic or therapeutic) of SPN is indicated? b) what type of surgical resection is required {lobectomy or limited (sublobar), lung resection such as wedge resection or anatomic segmentectomy} for malignant SPN? and c) by what method (VATS or open thoracotomy) should be performed biopsy-resection of SPN?

METHODS

We conducted a computerized literature search in the major medical databases (PubMed, EMBASE, OVID), to find systematic reviews, randomized control trials, retrospective studies and other relevant articles in English published from 1990 to 2015. The relevant to our review subject terms or key words occurred during our initial literature investigation were: solitary pulmonary nodule, coin lesion, non-small cell lung cancer, wedge resection, segmentectomy, limited or sublobar resection, lobectomy, video-assisted thoracic surgery, and thoracotomy. The above selected search terms were based on typical key words and on survey on the reference lists of relevant articles and publications.

RESULTS

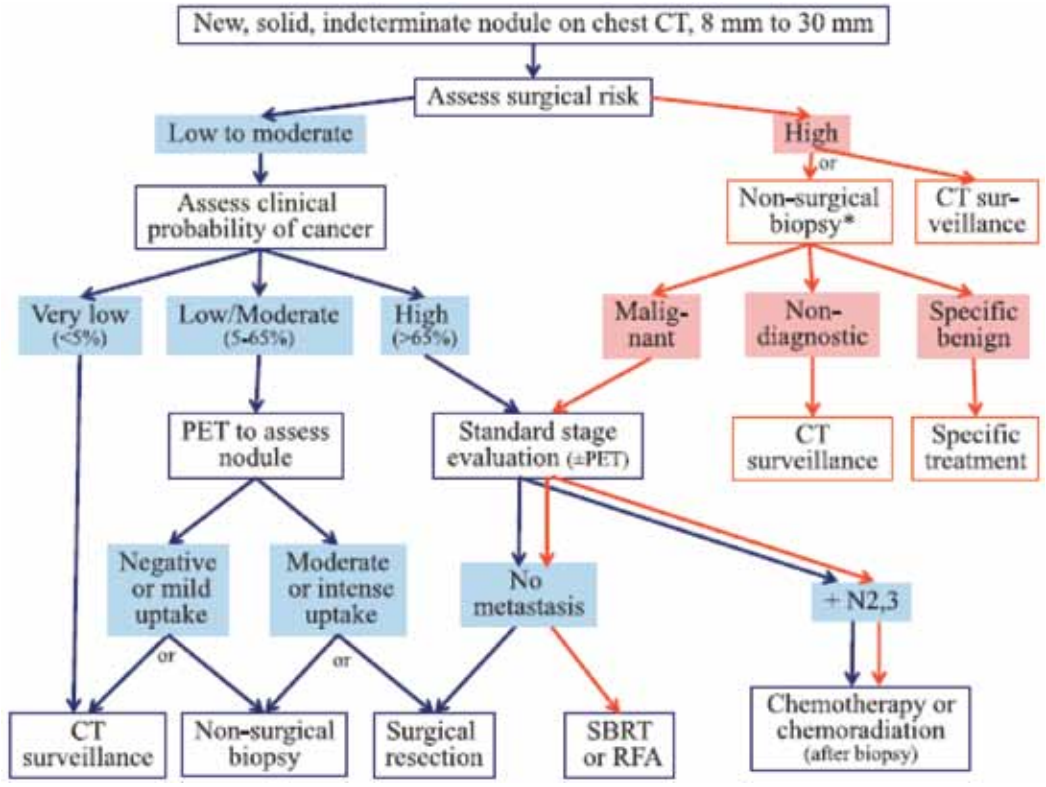
A) When is surgical resection (diagnostic or therapeutic) of SPN indicated?

Regarding the indications for surgical biopsy-resection of SPN we selected three articles, as the most relevant to our review, the basic recommendations and guidelines of which are widely accepted and recognized internationally as the most effective for SPN management. As shown in Table 1, where we quoted features of the above articles, Macmahon and colleagues, in 2005, recommended with the approval of the scientific community Fleischner, the first guidelines on the management of SPN up to 8 mm, diagnosed by computed tomography[2]. In 2007, Gould and colleagues, presented clinical practice guidelines, working for the American College of Chest Physicians, with 29 proposals on SPN management[3]. The same group of authors (Gould and colleagues), in 2013, published the latest and most up to date proposals on SPN management and presented also a useful algorithm summarizing the latest monitoring strategy for diagnosis and treatment of SPN[4]. From these three studies it was established that patients with SPN must be evaluated by using existing imaging and invasive diagnostic methods and depending on the possibility of malignancy of the SPN either staying in monitoring or if the above methods fail to set histological diagnosis, taking into account the risks of proposed and personalized surgical diagnosis and treatment methods of SPN, always based on guidelines and depending on their personal preferences too.

B) What type of surgical resection is required for malignant SPN [lobectomy or limited (sublobar) lung resection such as wedge resection or anatomic segmentectomy]?

Approaching the question whether lobectomy or sublobar resection of lung parenchyma is the best treatment approach for SPN, diagnosed to be NSCLC, intraoperatively, we found in the literature 286 articles of which we selected 8 as more relevant to our review. SPNs due

TABLE 1. Summary of recommendations and guidelines for management of solitary pulmonary nodule

Reference	**- Summary of guidelines and recommendations for solitary pulmonary nodule (SPN) management**		
MacMahon et al. (2005), Radiology	*- Recommendations for monitoring and management of SPN ≤8 mm detected accidentally on chest CT:*		
	SPN size	**Low-risk patients**	**High-risk patients**
	<4 mm	No need to follow up	Follow up CT at 12 months. If no change need no follow up
	4-6 mm	Follow up CT at 12 months. If no change need not follow up	Initial follow up CT at 12-24 months and at 18-24 months if no change
	6-8 mm	Initial follow up CT at 12-24 months and at 18-24 months if no change	Initial follow up CT at 3-6 months and then at 9-12 and 24 months if no change
	> 8 mm	Follow up CT at 3, 9 and 24 months then CT with iv contrast, PET scan, and ± biopsy	Follow up CT at 3, 9 and 24 months after CT with iv contrast, PET scan, and ± biopsy
Gould et al. (2007), CHEST	*- The guidelines related to SPN 8-30 mm, and multiple nodules when they are accidentally discovered during SPN investigation with emphasis on:* (1) assessment of risk factors for the probability of malignancy (2) value of imaging techniques (e.g. old chest X-rays), (3) evaluation of advantages and disadvantages of SPN management methods (e.g. observation, biopsy), and (4) weight to the preferences of each patient …. *- Surgical biopsy-resection in patients with SPN (8-10 mm) is recommended when:* (1) probability of malignancy moderate to high (> 60%), (2) hypermetabolic nodule in PET-scan (3) the fully informed patient wishes		
Gould et al. (2013), CHEST			

*CT: computerized tomography; PET-scan: positron emitted tomography scan; SBRT: stereotactic body radiation therapy; RFA: radio-frequency ablation;

to small cell lung cancer or metastases were beyond the object of our survey. The authors, year, journal, and type of publication, patient groups studied, and most relevant results, of the selected articles are summarized in Table 2a.

We started with the known randomized controlled study of Ginsberg and Rubinstein of 1995, where in contrast both with other studies of its time, and subsequent, it was reported that limited lung resection was associated with higher rates of local recurrence, and cancer associated mortality, without offering better rates of postoperative mortality, morbidity or ultimate preservation of lung function as regards to lobectomy. This study was commented critically in terms of correct conclusions as it had insufficient data on mediastinal lymph node sampling, the average follow-up was only 4.5 years, and 5-year survival was calculated from survival curves[5]. Then we included the meta-analysis of Nakamura and colleagues, who, in 2005, studying 2790 patients (although with significant data heterogeneity, which made difficult their evaluation), found no statistically significant differences in the survival of patients with SPN, proved NSCLC, who underwent lobectomy or limited resection[6]. In 2006, Okada and coworkers, in an important prospective randomized study with two groups of patients with SPN, demonstrated to be NSCLC, and without data of variable heterogeneity, wherein 262 underwent lobectomy, and 305 sublobar resection, managed to reverse the results of Ginsberg and Rubinstein as they reported that overall and disease-free survival, local recurrences rates, and prognosis in patients undergoing lobectomy or sublobar resection were similar[7]. In 2006, El-Sherif and colleagues, studied retrospectively 784 patients with SPN, proved NSCLC, of whom 577 underwent lobectomy and 207, with cardiopulmonary impairment, underwent sublobar resection. They observed that in patients with sublobar resection local recurrences rates were similar, and disease-free survival did not differ significantly (p=0.24), as opposed to overall survival rate (p=0.004), which was significantly lower, probably due to the comorbidities[8]. In another retrospective study Sienel and coworkers, in 2008, compared the survival of 87 patients with SPN, proved NSCLC, who underwent sublobar resections, due to cardiopulmonary impairment, of which 31 were wedge resections with lymph node sampling, and 56 were anatomical segmentectomies with systematic lymph node dissection, during a 17-year period. The two groups not only had no significant differences in sex, age, histology, tumor size, postoperative complications and other parameters, but regardless 5-year survival rates of patients undergoing segmentectomies, as compared with those undergoing wedge resections (80% vs 48%, p=0.005), cancer associated mortality rates (29% vs 52%, p=0.016), and local recurrences rates (16% vs 55%, p=0.001), had statistically significant differences. Therefore, it was established that patients' survival studies with SPN due to NSCLC, undergoing sublobar resection, should separate the segmentectomies from wedge resections[9]. Similarly to the aforementioned studies, De Giacomo and colleagues, in 2009, comparing retrospectively the outcome of 152 patients with SPN, proved NSCLC, of whom 116 underwent lobectomy and 36 sublobar resection, due to advanced age and comorbidities, reported that survival rates (64.4% vs 66.7%, p=0.3), had no statistically significant difference in contrast to local recurrences rates (6.9% vs 25%, p=0.006)[10]. In 2009, Rami-Porta and Tsuboi, published an important systematic review and meta-analysis with regard to the management of SPN that was intraoperatively proven NSCLC. The authors based on the results of eleven retrospective and three prospective non-randomized studies, and reported recommendations and guidelines concerning specifically patients who cannot tolerate lobectomy due to cardio-respiratory impairment, and have to undergo sublobar resection, which underwent insignificant modifications by subsequent reviews; therefore, we presented a summary of these separately in Table 2b[11]. In 2012, Wolf and colleagues, in a retrospective study of 238 patients with SPN due to NSCLC, of whom 84 underwent lobectomy and 154 sublobar resection, noted that lobectomy was associated with significantly higher rates of overall (p=0.0027) and disease free (p=0.0496) survival; they also reported that patients who underwent sublobar resection were older (p <0.0001), had worse lung function (p <0.00014), and although there was a trend towards higher local recurrences rates (16% vs 8%, p=0.1117), there was no difference in distant metastases rates, and additionally, when lymph node sampling was performed with sublobar resections, local recurrence rates and overall and disease-free survival rates were similar to those after lobectomy[12]. Finally, De Zoysa and coworkers, in 2012, by performing an international literature review, which included 16 studies of which a meta-analysis and a randomized controlled trial, concluded that wedge resections compared to anatomic segmentectomies were associated with lower survival rates, and higher recurrence rates, and that lobectomy should be preferred in younger patients with adequate cardiopulmonary reserves despite the fact that sublobar resection is associated with lower morbidity rates and shorter hospital stay; on the contrary, sublobar resection is associated with comparable to lo-

TABLE 2A. Studies on the type of surgical resection required positive for malignancy solitary pulmonary nodule (lobectomy or sublobar lung resection)

Reference	Patients' Groups	Survival	Local recurrences	Comments
Ginsberg and Rubinstein (1995) ATS randomized control study	Lobectomy: 125 Sublobar resection (Wedge or anatomical segmentectomy): 122	Lobectomy: 69.6% Sublobar resection: 60.65%	Lobectomy: 6.4% Sublobar resection: 17.2% (p=0.008)	30% increase in death rates with limited resection (p=0.08) and 300% increase in local recurrence rates (p=0.008)
Nakamura et al (2005) CANCER Systematic review and meta-analysis	Lobectomy: 1887 Sublobar resection: 903	5-year survival difference: 3.6%	Not mentioned	No statistically significant difference in survival rates
Okada et al. (2006) TCVS Prospective non randomized study	Lobectomy: 262 Sublobar resection: 305	Lobectomy: 89.1% Sublobar resection: 89.6%	Lobectomy: 6.9% Sublobar resection: 4.9%	Disease-free 5-year survival: Lobectomy: 83.4% Sublobar resection: 85.9%
El-Sherif et al (2006) ATS Retrospective study	Lobectomy: 577 Segmentectomy: 85 Wedge resection: 122	Lobectomy: 54% Sublobar resection: 40%	Lobectomy: 8% Sublobar resection: 14%	No statistically significant difference in disease-free survival (p=0.24)
Sienel et al (2008) EJCTS Retrospective study	Segmentectomy: 56 Wedge resection: 31	Segmentectomy: 71% Wedge resection: 48% (p=0.016)	Segmentectomy: 16% Wedge resection: 55% (p=0.001)	Distant metastases: 18% after segmentectomy and 10% after wedge resection (p=0.53)
De Giacomo et al (2009) SJS Retrospective study	Lobectomy: 116 Sublobar resection: 36	Lobectomy: 64% Sublobar resection: 66.7%	Lobectomy: 1.7% Sublobar resection: 5.5%	Rates of distant metastases: 24% after lobectomy and 11% after sublobar resection (p=0.14)
Wolf et al (2012) ICVTS Retrospective study	Lobectomy: 84 Sublobar resection: 154	Lobectomy: 80% Sublobar resection: 59% (p=0.0027)	Lobectomy: 8% Sublobar resection: 16% (p=0.11)	5-year recurrence-free survival: Lobectomy: 87% Sublobar resection: 74% (p=0.049)
De Zoysa et al (2012) ICVTS Systematic review and meta-analysis	Lobectomy: 14389 Sublobar resection (wedge or anatomical segmentectomy): 3115	lobectomy: 54-90% Sublobar resection: 40-89%	Lobectomy: 1.3 to 19% Wedge resection: 15.5-30% Segmentectomy: 2.7 to 22.7%	No statistically significant difference in survival rates, but in local recurrence rates (especially after wedge resection)

bectomy results in patients >71 years and in those with small, peripheral SPN[13].

C) By what method (VATS or open thoracotomy) should be performed biopsy-resection of SPN?

Attempting to answer the question whether VATS or

TABLE 2B. Summary of guidelines relating to the type of surgical resection recommended for malignant solitary pulmonary nodule

Reference	Summary of Guidelines
Rami-Porta and Tsuboi (2009) ERJ Systematic Review and Meta-analysis	(1) Sublobar resections should be avoided in patients with NSCLC, T1N0M0, who can tolerate lobectomy because although they are associated with no significantly different survival they present >local relapse rates (Degree of recommendation: A)
	(2) Sublobar resection is an alternative that can have similar prognosis in patients who cannot tolerate lobectomy (Degree of recommendation: B)
	(3) When sublobar resection is the only a patient can tolerate then anatomic segmentectomy is a better option than wedge resection because of higher survival and lower local recurrences rates (Degree of recommendation: B)
	(4) Anatomical segmentectomy if feasible should be performed in tumors <2 cm in diameter (as it has comparable to lobectomy results), while in tumors >2cm lobectomy should be preferred (Degree of recommendation: B)
	(5) Wedge resection should be preferred in patients >71 years as it has similar to lobectomy results (Degree of recommendation: B)
	(6) Regarding both anatomic segmentectomy and wedge resection surgical resection margins should be at least 1 cm width (Degree of recommendation: B)
	(7) If wedge resection is the only resection a patient can tolerate then postoperative radiotherapy is recommended (Degree of recommendation: B)
	(8) If an intraoperative diagnosis of bronchiole-alveolar carcinoma is guaranteed in SPN <2cm, due to the non-invasive nature of this tumor and the abnormal lymph infiltration sublobar resection without lymph node dissection can be sufficient (Degree of recommendation: B)

open thoracotomy is the best diagnostic or therapeutic surgical procedure for patients with SPN we came across 252 articles, in the literature, of which we selected five, three reviews and two retrospective studies, that best served our aim. The authors, year, journal, and type of publications, patients groups studied, and the most relevant to our study results, are summarized in Table 3.

In 2008, Whitson and coworkers, reviewed 39 publications, comparing 3256 patients with SPN due to NSCLC, who underwent open thoracotomy lobectomy with 3114 who underwent VATS lobectomy (without significant differences in their characteristics). They observed that complication rates after VATS lobectomy were significantly lower than those of open thoracotomy lobectomy; and although there was not enough data on the conducted lymph node dissection and local recurrences, VATS lobectomy was associated with a statistically significant lower mean duration of hospitalization (p=0.016), and longer survival than the open thoracotomy lobectomy (p=0.064)[14]. In 2012, Zhang and colleagues, in a review and meta-analysis of 21 publications with 2380 patients with SPN proved NSCLC, who underwent VATS lobectomy, and 3009 who underwent open thoracotomy lobectomy, compared the results relating to systematic mediastinal lymph node dissection (LND), versus lymph node sampling (LNS), rates of distant metastases, local recurrences and patients' survival and concluded that: a) there was no statistically significant difference in the number of removed or examined lymph nodes in patients undergoing LND or LNS between the two patient groups (p=0.14), b) distant metastases rates and local relapse was significantly lower in the VATS group (p <0.01 and p=0.03, respectively), as opposed to 5-year survival rate (p <0.01), which was significantly higher in the VATS group too[15]. Regarding anatomic segmentectomies performed in patients with SPN, proved NSCLC, Schuchert and colleagues, in 2009, studied retrospectively 104 patients underwent VATS anatomic segmentectomies 121 underwent open thoracotomy anatomic segmentectomies (without significant differences in their characteristics), and noted that: a) there were two perioperative deaths (0.9%), only in the thoracotomy group, b) hospitalization and morbidity were significantly shorter (p <0.001, and p=0.016, respectively) for the VATS group, and c) relapse rates (p=0.10) and overall survival (p=0.605) did not differ significantly between the two groups[16]. In another literature review and meta-analysis, Linden and colleagues, in 2014, concluded that VATS anatomic segmentectomy was

TABLE 3. Studies related to the preferred method (VATS or open thoracotomy) for surgical biopsy-resection of the solitary pulmonary nodule

Reference	Patients' Groups	Survival	Complications	Results
Whitson et al (2008), ATS Systematic Review and Meta-analysis	Thoracotomy: 3256 VATS: 3114	5-year survival: - Thoracotomy: 65.6% - VATS: 80.1% (p=0.064)	- Thoracotomy: 31.2% - VATS: 16.4% (p=0.018)	Average length of stay (days): - Thoracotomy: 13.3 - VATS: 8.3 (p=0.016)
Zhang Z. et al (2012), EJCTS Systematic Review and Meta-analysis	Thoracotomy: 3009 VATS: 2380	Significantly higher survival rates (RR: 1.10; CI: 1.04-1.17, p<0.01), found in the VATS group	The relative risk of distant metastases (RR: 0.61; 95% CI: 0.48-0.78; p<0.01) and local recurrences (RR: 0.66; 95% CI: 0.46-0.95; p<0.03) were significantly lower for the VATS group	No significant differences in the number of lymph nodes examined between the two groups (p=0.14)
Schuchert et al, (2009), JTCVS Retrospective study	Anatomic segmentectomy with Thoracotomy: 121 Anatomical segmentectomy with VATS: 104	No differences in disease-free (p=0.996) or overall survival (p=0.605) Relapses: - Thoracotomy: 24% - VATS: 16%	- Thoracotomy: 61.15% - VATS: 44.23% (p=0.016)	Average length of stay (days): - Thoracotomy: 7 - VATS: 5 (p=0.01) Average number of resected lymph nodes - Thoracotomy: 9.1 - VATS: 6.4 (p=0.003)
Linden et al (2014), ICVTS Systematic Review and Meta-analysis	- Anatomic segmentectomy with Thoracotomy: 201 - Anatomic segmentectomy with VATS: 312	No significant differences in 5-year disease-free and overall survival	Complications: - Thoracotomy: 30% - VATS: 15-25% Conversion rates in open surgery: 0-2%	Greatest difference in average length of stay (days): - Thoracotomy: 8.3 - VATS: 3.5
Ghaly et al (2016), ATS Retrospective study	Anatomic segmentectomy with Thoracotomy: 102 Anatomical segmentectomy with VATS: 91	5-year overall survival: - Thoracotomy: 62% - VATS: 75% (p=0.017) 5-year disease-free survival: - Thoracotomy: 47% - VATS: 58% (p=0.013)	Pulmonary complications: - Thoracotomy: 26.5% - VATS: 13.2% (p=0.022)	Average length of stay (days): - Thoracotomy: 5, - VATS: 4 (p=0.001) Average number of lymph node sampling: - Thoracotomy: 8 - VATS: 7 (p=0.104)

an appropriate alternative to open thoracotomy anatomic segmentectomy with respect to morbidity, survival and 'oncology' equivalence in patients with SPN due to NSCLC, as they studied 312 patients underwent VATS anatomic segmentectomy and 201 submitted to open thoracotomy anatomic segmentectomy. They also reported no statistically significant differences in overall survival (p=0.605) and disease-free survival (p=0.996) between the two groups[17].

In 2016 Ghaly and coworkers, studying retrospectively 91 patients with SPN due to NSCLC, who underwent VATS anatomic segmentectomy and 102 underwent open thoracotomy anatomic segmentectomy {without significant differences, except for mean age (p=0.016), in their characteristics, nor in the postoperative pathological stage (p=0.439), or in mediastinal lymph node sampling number (p=0.234)}, observed significantly lower mean

duration of hospitalization (p=0.001), fewer pulmonary complications (p=0.02), and higher 5-year disease-free survival (p=0.013) and overall survival (p=0.017), in the VATS group[18].

DISCUSSION

A plethora of diagnostic non-invasive methods have been used in the differential diagnosis of SPN, and in particular to distinguish between benign or malignant. Clinical and imaging parameters that determine the likelihood of malignancy of the SPN are a) related to the patient, such as age, smoking, hemoptysis, prior history of malignancy, and b) associated with the SPN such as maximum diameter, location, boundaries, contour, rate of size increase (previous chest x-rays), wall thickness, calcification patterns, contrast enhancement after administration of contrast in chest CT and intake of radio-labeled glucose in PET-scan. In 1997, Swensen and colleagues, proposed a clinical assessment model of SPN potential for malignancy through three clinical and radiological variables: $e^x / (1 + e^x)$, where e is the base of natural logarithms and x=-6.8272 +0.0391 (age) +0.7917 (smoking) +1.3388 (cancer) +0.1274 (diameter) +1.0407 (spikes) +0.7838 (SPN in the upper lung lobe)[19]. In addition to imaging methods important is the contribution of bronchoscopy, especially for centrally located SPN, when combined with various biopsy or cytological methods, such as transbronchial needle aspiration biopsy (TBNA), in visible lesions or bronchial 'brushing' or broncho-alveolar washing in non-visible lesions. In addition to conventional invasive procedures such as fine needle aspiration biopsy (FNAB), under CT guidance, new diagnostic and interventional procedures have been developed such as virtual bronchoscopy with 3-D reconstruction of images from a CT scanner, guided electromagnetic navigation bronchoscopy (ENB), bronchoscopy with endobronchial ultrasound (EBUS), which can also be combined with biopsy or aspiration of cells. As regards to surgical diagnosis and treatment of an undiagnosed SPN, either with VATS or with open thoracotomy, a biopsy-resection is initially performed by wedge resection of SPN sent for frozen section. If this is negative for malignancy nothing needs to be done further, and closure of incisions, in anatomical layers, follows in order to complete the operation. However, if frozen section is positive for malignancy there are the following options: a) no more than the wedge resection needs to be done if surgically contraindicated (solitary metastasis or presence of positive mediastinal lymph nodes) or the patient cannot tolerate it due to comorbidities, b) proceed to anatomic segmentectomy which although is considered limited lung resection, in the literature it seems to be associated with similar to lobectomy rates of 5-year survival, local recurrences, complications, and duration of hospitalization, and c) lung lobectomy which is considered the most oncologically adequate procedure for patients with SPN proved NSCLC.

Studying the literature, we found that indications for surgical intervention in the context of SPN investigation are quite well defined, and with the existing evidence-based guidelines constitute the most important tools for the clinician, in terms of SPN management strategy. Generally, the increased probability of malignancy of the SPN, and the inability to set histological diagnosis with the less invasive diagnostic methods, are the two most important factors that lead to surgical intervention, diagnostic or therapeutic, taking always into account the personal preference of the patients too. As regards benign SPN, diagnosed intraoperatively, and metastatic lung nodules, wedge resection or even nodule enucleation is sufficient[2-4]. If the SPN is due to NSCLC the question whether lobectomy or sublobar resection (anatomic segmentectomy or wedge resection) is the best therapeutic approach our review revealed the following: a) lobectomy appears to remain the most acceptable resection primarily for young patients with adequate cardiopulmonary function, b) for patients >70 years of age or those with limited cardiopulmonary function, it appears that sublobar resections may be comparable with lobectomy regarding survival rates, but wedge resections although have the advantages of lower related morbidity and shorter hospital stay, as compared to lobectomy, are associated with more local recurrences, c) anatomic segmentectomies should be distinguished from wedge resections because in the literature they have been associated with comparable to lobectomies results, regarding their oncological adequacy, as well as rates of local recurrences and survival of patients with SPN, proved intraoperatively NSCLC, except from specific types of NSCLC with less invasive nature, such as bronchiole-alveolar carcinoma, that are sufficiently addressed with wedge resections[5-13].

Attempting to answer the question whether sublobar resection or lobectomy performed via VATS or open thoracotomy is the best diagnostic and therapeutic method for patients with SPN due to NSCLC, our review showed that lobectomy or sublobar resections performed by VATS in comparison to those performed by open thoracotomy

are associated with lower rates of mortality, morbidity (particularly pulmonary complications), recurrences, and shorter hospitalization; in centers with experience VATS resections despite technical difficulties are oncologically equivalent, and safe and should be preferred in patients with compromised cardiopulmonary function[14-19].

In conclusion, although answers were given to the questions we raised in our review there are limitations such as data and results heterogeneity of different publications (retrospective, prospective, reviews), that we have included in our review as well as the different objectives set by their authors, and the fact that they are to some extent influenced by the experience and the common practice of surgeons in the centers they were performed. Therefore, it is necessary to conduct further blinded and randomized controlled studies so as to compare on the one hand lobectomies and sublobar resections performed by the VATS approach with those performed by open thoracotomy, and on the other hand sublobar resections with lobectomies separately, whether they are appropriate for patients' management with SPN proved NSCLC.

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