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Review / Derleme

Extended pneumonectomy for advanced lung cancer with cardiovascular structural invasions

Kardiyovasküler yapısal invazyonları olan ileri akciğer kanseri için genişletilmiş pnömonektomi

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ABSTRACT

Background: This study aims to investigate the predictive factors in relation to tumor stages, mediastinal involvements, perioperative adjuvant therapies and surgical techniques in advanced lung cancer patients who underwent extended pneumonectomy with cardiovascular structural resection.

Methods: A comprehensive literature review was performed for extended pneumonectomies with cardiovascular structural resections in the PubMed, Google Scholar and HighWire Press for the year range 2000-2016. Data were carefully extracted regarding details such as the study population, demographics, clinical features, types of lung cancer, pathologic stages, nodal involvement, extent of pneumonectomy, cardiovascular structural resections, use of cardiopulmonary bypass, completeness of resection, pre- and postoperative adjuvant therapies, 1-5-year survival, median survival duration, comorbidity and mortality.

Results: Patients undergoing extended pneumonectomy with cardiovascular structural resection were characterized more by squamous carcinomas, N_0 or N_1, T_4, stage 3 and left atrial invasions. More patients received postoperative radiochemotherapy than radio- or chemotherapy. The five-year survival rate was 30.5±11.5% and the median survival duration was 23.0±10.7 months. Level 1 left atrial, aortic adventitial, and partial superior vena cava resections could be performed without cardiopulmonary bypass, while levels 2 and 3 left atrial resections with aorta or superior/inferior vena cava replacement should be performed under cardiopulmonary bypass.

Conclusion: The advent of cardiopulmonary bypass facilitated complete resection of lung cancer, while leading to potential risks of metastasis and reoccurrence. Pathological status, surgical techniques and pre- and postoperative adjuvant therapies affect survival significantly. Surgical indications and negative predictive risk factors for patients' survival warrant further evaluations.

Keywords: Cardiopulmonary bypass; lung neoplasms; neoplasm metastasis; pneumonectomy.

ÖZ

Amaç: Bu çalışmada kardiyovasküler yapısal rezeksiyon ile genişletilmiş pnömonektomi uygulanan hastalarda tümör evrelerine ilişkin belirleyici faktörler, mediastinal tutulumlar, perioperatif adjuvan terapiler ve cerrahi teknikler araştırıldı.

Çalışma planı: PubMed, Google Scholar ve HighWire Press'te 2000-2016 yıl aralığı için kardiyovasküler yapısal rezeksiyonlar ile genişletilmiş pnömonektomiler için kapsamlı bir literatür derlemesi yapıldı. Çalışma popülasyonu, demografikler, klinik özellikler, akciğer kanseri türleri, patolojik evreler, nodal tutulum, pnömonektomi boyutu, kardiyovasküler yapısal rezeksiyonlar, kardiyopulmoner baypas kullanımı, rezeksiyonun tamlığı, ameliyat öncesi ve sonrası adjuvan terapiler, 1-5 yıllık sağkalım, medyan sağkalım süresi, komorbidite ve mortalite gibi ayrıntılarla ilgili veriler dikkatle çıkartıldı.

Bulgular: Kardiyovasküler yapısal rezeksiyon ile genişletilmiş pnömonektomi uygulanan hastalar daha fazla skuamöz karsinomalar, N_0 veya N_1, T_4, evre 3 ve sol atriyal invazyonlar ile karakterize idi. Radyoterapi veya kemoterapiye göre daha fazla hasta ameliyat sonrası radyokemoterapi aldı. Beş yıllık sağkalım oranı %30.5±11.5 ve medyan sağkalım süresi 23.0±10.7 ay idi. Düzey 1 sol atriyal, aortik adventisya ve parsiyel superior vena kava rezeksiyonları kardiyopulmoner baypas olmaksızın yapılabilir iken aort veya superior/inferior vena kava replasmanı ile düzey 2 ve 3 sol atriyal rezeksiyonları kardiyopulmoner baypas altında uygulanmalıdır.

Sonuç: Kardiyopulmoner baypasın gelişimi akciğer kanserinin tam rezeksiyonunu kolaylaştırmakla beraber potansiyel metastaz ve nüks risklerine neden olmaktadır. Patolojik durum, cerrahi teknikler ve ameliyat öncesi ve sonrası adjuvan terapiler sağkalımı anlamlı şekilde etkilemektedir. Cerrahi endikasyonlar ve hastaların sağkalımı için negatif belirleyici risk faktörleri daha ileri değerlendirmeler gerektirmektedir.

Anahtar sözcükler: Kardiyopulmoner baypas; akciğer neoplazmları; neoplazm metastazı; pnömonektomi.

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Direct invasion of primary lung cancer to the heart, particularly the left atrium, occurs in up to 10% of primary lung cancer patients.[1] It has been recognized since 1963 that patients with tumor invasion of myocardium may be associated with Adams-Stokes syndrome.[2] More and more clinical observations have disclosed that patients may present with arrhythmia, heart failure or myocardial infarction.[3] In 1967, Ruggieri[4] firstly reported three cases of pneumonectomy with resection of the left atrium under cardiopulmonary bypass (CPB) and succeeded in one of the patients. Since then, extended pneumonectomy with or without the use of CPB was increasingly reported with significantly improved survival rates.[5]

It has been noted that the prognoses of lung cancer patients correspond significantly with the stage of lesions and treatment choices. Surgical resection of the tumors seems to be a promising treatment method in patients with lung cancer of certain stage, and complete resection of the tumors may be associated with an enhanced survival rate.[6] Nevertheless, the surgical indications for advanced lung cancers that invade the surrounding structures remain a challenge to the surgeons.[6] The application of CPB in malignant cancer patients remains a debate due to the potential adverse effects of CPB in cancer metastasis, reoccurrence and patients' prognoses.[7] The patients with a planned CPB for lung cancer resection showed a higher survival rate than those with an unplanned or emergent CPB.[8]

The pertinent predictive factors in relation to tumor stages, mediastinal involvements, perioperative adjuvant therapies and surgical techniques[9] have not been fully evaluated. Generally speaking, the prognoses of such patients remain unknown. Therefore, in this study, l aimed to investigate the predictive factors in relation to tumor stages, mediastinal involvements, perioperative adjuvant therapies and surgical techniques in advanced lung cancer patients who underwent extended pneumonectomy with cardiovascular structural resection.

MATERIALS AND METHODS

Comprehensive retrieval of the literature of extended pneumonectomy with cardiovascular structural resection was performed in the PubMed, Google Scholar and HighWire Press for the year range 2000-2016.

Search terms included "extended pneumonectomy", "primary lung cancer", "mediastinal involvements", "heart", "left/right atrium", "ventricle", "aorta", "pulmonary artery/vein", "superior/inferior vena cava" and "cardiopulmonary bypass". Articles mentioning extended pneumonectomy but lacking significant patient information were excluded.

Data were carefully extracted for details such as the study population, demographics, clinical features, types of lung cancer, pathologic stages, nodal involvement, extent of pneumonectomy, cardiovascular structural resections, use of CPB, completeness of resection, pre- and postoperative adjuvant therapies, 1-5-year survival, median survival duration, comorbidity and mortality.

Statistical analysis

Measurement data were expressed in mean ± standard deviation with range and median values and were compared by independent sample t-test. Categorical variables were compared by Fisher exact test. A p value <0.05 was considered statistically significant.

RESULTS

Between 2000 and 2016, 22 articles on the subject of extended pneumonectomy were collected,[1,5,6,9-27] including 14 (63.6%) original articles and eight (36.3%) case reports, with a total of 619 patients involved. In 21 reports, patients' age was reported with a median age of 69 years (range, 18-81 years). Patient's gender was recorded for 421 patients (68.0%): 331 (78.6%) were males and 90 (21.4%) were females with a male-to-female ratio of 3.7:1. The exact locations of the lung cancers were described for 56 patients: right lower/right middle lobe in 20 patients (35.7%),[9,18,24] right upper lobe in 19 patients (33.9%),[9] left lower lobe in nine patients (16.1%),[9,19,20] main stem bronchus in seven patients (12.5%),[9] and right hilum in one patient (1.8%).[13]

Pathological classifications of the lung cancers were reported for 575 patients (92.9%): 336 (58.4%) were squamous carcinomas, 153 (26.6%) were adenocarcinomas, 37 (6.4%) were large cell carcinomas, nine (1.6%) were sarcomas (one of the patients had sarcoma plus squamous carcinoma of the lung), eight (1.4%) were non-small cell carcinomas, seven (1.2%) were adenosquamous carcinomas, three (0.5%) were undifferentiated, two (0.3%) were small cell carcinomas and 21 (3.7%) were other types of lung cancers.

Clinical N status ($N_0/N_1/N_2$) was reported in 19 reports[1,5,9,11-26] for 112 patients: N_0 (n=26, 23.3%), N_1 (n=19, 17.0%), $N_0/_1$ (n=35, 31.3%), and N_2 (n=32, 28.6%). There were more cases with N_0 or N_1 than those with N_2 (χ^2=41.1, p<0.001).

Table 1. Cardiovascular involvements of primary lung cancers in 488 patients

Cardiovascular involvement	n	%
Single location involvement	475	97.3
Heart	176	37.1
LA	126	71.6
RA	1	0.6
Atrium, unspecified	34	19.3
Heart, unspecified	15	8.5
Great vessels	299	62.9
PA	90	30.1
PV	77	25.8
SVC	55	18.4
Aorta	16	5.4
Great vessels, unspecified	61	5.4
Multiple location involvements	13	2.7
LA + PV	4	30.8
Atrium + SVC	1	7.7
IAS + LA + RA	1	7.7
LA + DA + PA	1	7.7
LA + PA	1	7.7
IAS + LA + RA + PV	1	7.7
LA + PA + PV	1	7.7
LA + RA + PV	1	7.7
LA + RA + RV + coronary artery + SVC	1	7.7
RVOT + PA	1	7.7

LA: Left atrium; RA: Right atrium; PA: Pulmonary artery; PV: Pulmonary vein; SVC: Superior vena cava; IAS: Intraatrial septum; DA: Descending aorta; RVOT: Right ventricular outflow tract.

T status was known in 493 patients:[1,5,6,9-27] T_1 (n=11, 2.2%), T_2 (n=33, 6.7%), T_3 (n=21, 4.3%), $T_{<3}$ (n=17, 3.4%) and T_4 (n=411, 83.4%). There were more T_4 than T_{1-3} (83.4% vs. 16.6%, χ^2=439.1, p<0.0001).

Pathologic stage was reported in 115 patients: stage 1 in two cases (1.7%), stage 2 in seven cases (6.1%) [including stage 2A in one case and stage 2B in three cases], stage 3 in 104 (90.6%) cases [including stage 3A in 41 cases and stage 3B in 20 cases] and stage 4 in two cases (1.7%) (χ^2=350.9, p<0.0001).

Cardiovascular involvements were described in 488 patients: 475 (97.3%) were single location involvement while 13 (2.7%) were multiple (χ^2=874.8, p<0.0001). Of the patients with single location involvement, the most common affected structure was the left atrium, followed by the pulmonary artery and pulmonary vein. There were more patients with great vessel (or branch) involvements than those with heart involvements (62.9% (299/475) vs. 37.1% (176/475), χ^2=63.7, p<0.0001). Of the patients with multiple location involvements, 13 patients had 35 cardiovascular structures invaded, including 19 heart and 16 great vessel (or branch) involvements. The detailed information of involvement locations was shown in Table 1. In total, there were 510 cardiovascular structural invasions including 318 (62.4%) heart and 192 (37.6%) great vessel involvements (χ^2=62.3, p<0.0001).

Table 2. Extent of pneumonectomy in 451 patients

Extent of pneumonectomy	n	%
Lung	350	61.0
Lobe	161	28.0
Bilobe	17	3.0
Sleeve	44	7.7
Segment	1	0.2
Wedge	1	0.2

Table 3. Cardiovascular structural resections

Cardiovascular structural resection	n	%
Single structure resection	368	81.6
Heart	174	47.3
Atrium	172	98.9
LA	134	77.9
RA	4	2.3
Atrium, unspecified	34	19.8
RV	2	1.1
Vessel	194	52.7
SVC	100	51.5
PA	71	36.6
Aorta	20	10.3
IVC	2	1.0
Coronary artery	1	0.5
Multiple structural resections	83	18.4
Carina + LA	35	42.2
Carina + SVC	27	32.5
Carina + aorta	14	16.9
Aorta adventitia + partial SVC	4	4.8
IAS + LA + RA	1	1.2
Atrium + SVC	1	1.2
LA + PA bifurcation	1	1.2

LA: Left atrium; RA: Right atrium; RV: Right ventricle; SVC: Superior vena cava; PA: Pulmonary artery; IVC: Inferior vena cava; IAS: Intraatrial septum.

Of the 451 extended pneumonectomies (Table 2), 64 patients (14.2%) were with the aid of CPB. The indications of CPB were described in 31 patients: it was left atrial resection in 23 patients (74.2%),[1,9,18-20] lateral resection of the aorta in one patient (3.2%),[12] complete aortic resection plus graft replacement in four patients (12.9%)[12] and left pulmonary artery ostium resection in three patients (9.7%).[9] Of the surgical techniques, aortic resections included aortic adventitial resection[9,14] and lateral aortic wall resection;[12] while superior vena cava resections included partial resection [12] and complete resection with graft replacement[12] (Table 3).

Completeness of tumor resection was described in 600 patients: R_0 (n=453, 75.5%) and R_1 (n=147, 24.5%) with an R_0/R_1 ratio of 3.1:1 (χ^2=312.1, p<0.0001).

A total of 180 patients received adjuvant preoperative radio- and (or) chemotherapy: 156 (86.7%) were chemo, four (2.2%) were radio- and

Table 4. Patients' prognosis

Prognosis	Report, (n)	Mean±SD	Range	Median	Reference
Postoperative comorbidity (%)	8	33.2±13.2	17-52.6	30.8	[5,10,12,14,16,17,23,27]
Operative mortality (%)	10	9.3±6.7	0-22	7.9	[5,6,10,12,14,16,17,22,23,26]
1-year survival (%)	6	63.5±11.8	46-80	63	[9,11,16,22,26,27]
3-years survival (%)	6	33.1±12.1	31-53	33	[9,11,16,22,26,27]
5-years survival (%)	13	30.5± 11.5	16-53	26.8	[5,6,10-12,14,16,17,22,23,25-27]
Median survival (month)	12	23.0±10.7	8.7-50	22.5	[5,10-12,16,22,23,25,26]

SD: Standard deviation.

20 (11.1%) were radio-chemotherapy (χ^2=348.8, p<0.0001). Ninety-eight patients received adjuvant postoperative radio- and (or) chemotherapy: 58 (59.2%) were chemo-, four (19.4%) were radio- and 20 (21.4%) were radio-chemotherapy (χ^2=44.3, p<0.0001).

Patients were under follow-up for 22.5±10.5 (range, 8-43; median, 19) months (n=17).[5,9-11,13-19,20-24,26] During the follow-up period, the number of deceased patients was reported in nine reports, which amounted up to 156 cases with a mortality of 25.2%.[1,9-15,17-22,24,26] Postoperative reoccurrence and metastasis were seen in 14[10,14,17] and 30 cases,[9,18] respectively. Patients' prognosis was shown in Table 4.

DISCUSSION

Lung cancer with cardiovascular invasions is often recognized to be incurable to surgical resections, and medical treatment of lung cancer is often associated with dismal outcomes.[5] In these circumstances, pneumonectomy is often insufficient for lung cancer resection.[10] Meanwhile, extended pneumonectomy could be a feasible option for primary lung cancer with mediastinal involvement with the advent of CPB.[28] The operation could be one-stage, carried out with the aid of CPB via standard median sternotomy.[1] Cardiovascular structural resections could be resected and reconstructed safely under CPB.[20] However, one of the major concerns is a transient immunosuppression with subsequent potential tumor metastasis and reoccurrence with the use of CPB in oncologic operations. A clinical study revealed that there might be a relationship, at most moderate, between CPB and cancer progression.[29] But it was evident that a planned CPB did not affect survival of patients undergoing extended pneumonectomy.[30]

The decision-making of the indications for extended pneumonectomy relies on preoperative computed tomographic scan and mediastinoscopy for tumor staging.[14] In animal experiments, the extent of left atrial resection for extended pneumonectomy was determined as one-third of the left atrium, which ensured a complete resection of the tumor.[31] This cutoff value has been verified in clinical practice.[32] Galvaing et al.[14] categorized left atrial resection into three levels: without interatrial septum dissection (Level 1), interatrial septum dissection without interatrial muscle sectioning (Level 2); and with both interatrial septum dissection and interatrial muscle sectioning (Level 3).

In view of lung cancer pathologies, better patient survival correlated with adeno- than squamous carcinoma (46.9% vs. 0%),[17] superior or inferior mediastinal involvements than those with both superior and inferior mediastinal involvements (35% vs. 25% vs. 0%, p=0.03),[9] and lung cancer of the upper lobe or of the main bronchus than of the lower lobe.[9] Mu et al.[33] reported an opposite trend with a highest five-year survival in N_0 in comparison to N_1 or N_2 (74% vs. 44.9% vs. 15.1%, p=0.028). The median survival of patients with an $N_{0/1}$ lesion was 16 months in contrast to 8.8 months of those with an N_2 lesion.[12] On the contrary, Pitz et al.[6] proposed that mediastinal nodal involvement worsen the prognosis, and the five-year survival rate was higher in patients with N_2 than in those with N_1 or N_0 (57.1% vs. 43.8% vs. 33.3%, p>0.05), as in their series, all N_0 patients had aorta involvement of lung cancer.[6] Multivariable analysis showed that the operative procedure, pathologic T status and nodal involvement were significant independent prognostic factors of lung cancer resection.[34] However, Borri et al.[10] stated that pathologic T status had no impact on survival (five-year survival: 22% for $T_{<4}$ vs. 26% for T_4, p>0.05). Moreover, types of invasion of either direct or lymph node invasion did not affect patient survival.[17]

There is consensus that the five-year survival rate was higher in patients with complete resection than those with incomplete resection (37.5-46.2% vs. 10.9-22.4%, p<0.05).[6,33] Incomplete resection was attributed to positive resection margin, positive lymph node, combined positive margin and lymph node, and malignant pleural effusions.[6] Kuehnl et al.[16] reported that completeness of tumor resection affected patients' survival. Surgical resection of cardiovascular structures: aorta resection vs. left/right atrium resection (44.4% vs. 0%), but no difference between use and unuse of CPB (38.1% vs. 14.3%).[17] Patient survival also depended on surgical procedures of choices. Patient survival was higher after sleeve lobectomy than that after pneumonectomy.[35] Nevertheless, Galvaing et al.[14] stated that type of operation (pneumonectomy vs. lobectomy), side of surgical resection, or completeness of resection did not affect patients' survival. They also suggested that for tumors invading the left atrium without extending to the intraatrial septum, extended pneumonectomy should be carried out without CPB.[14] They found that *en bloc* resection of the tumor invading the intraatrial septum could be safely performed with no hemodynamic disturbances.

Adjuvant postoperative radiation played an important role in enhancing patients' survival. Bernard et al.[9] reported that the three-year survival rate of patients with adjuvant postoperative radiation was higher than those without (30% vs. 16%, p=0.05),

and an improved survival was also observed in patients with surgical resection with chemo- and radiotherapies. However, Kusumoto et al.[17] reported that there was no difference between patients receiving or not receiving down-staging induction therapy (50% vs. 0%).

The limitation of this study is that concerning the limited number of reports as well scantiness of randomized control studies, the information in the present article seems to be lacking the necessary data to reach a definite conclusion. Thus, further studies are warranted to achieve more substantial information.

In conclusion, extended pneumonectomy with cardiovascular structural resection in advance lung cancer patients is a challenging procedure. The advent of cardiopulmonary bypass has facilitated complete resection of the cancer, while causing risks for potential metastasis and reoccurrence. Level 1 left atrial, aortic adventitial, and partial superior vena cava resections could be performed without cardiopulmonary bypass, while levels 2 and 3 left atrial resection and aorta or superior/inferior vena cava replacement should be carried out under cardiopulmonary bypass. Pathological status, surgical procedure of choices and pre- and postoperative adjuvant therapies impact on survival significantly. Surgical indications and negative predictive risk factors for patients' survival warrant further evaluations.

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