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Prognostic factors for survival after complete resections of synchronous lung cancers in multiple lobes: pooled analysis based on individual patient data

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Background: Some reports suggest that patients with synchronous multiple foci of nonsmall-cell lung cancers (NSCLC) distributed in multiple lobes have a poor prognosis, even when there is no extrathoracic metastasis. The vast majority of such patients do not receive surgical treatment. For those who undergo surgery, prognostic factors are unclear.

Patients and methods: We systematically reviewed the literature on surgery for synchronous NSCLC in multiple lobes published between 1990 and 2011. Individual patient data were used to obtain adjusted hazard ratios (HRs) in each dataset and pooled analyses were carried out.

Results: Six studies contributed 467 eligible patients for analysis. The median overall survival was 52.0 months [95% confidence interval 45.6–63.7]. Male gender and advanced age were associated with a decreased survival: HRs 1.64 (1.22, 2.22) and 1.40 (1.20, 1.80) per 20-year increment, respectively. Patients with cancers distributed in one lung had a higher mortality risk than those with bilateral disease: HRs 1.45 (1.06, 2.00). N1 or N2 had a decreased survival compared with N0: HRs 1.68 (1.12, 2.51) and 1.94 (1.33, 2.82), respectively. There was a trend toward increased mortality among patients with different histology: HRs 1.29 (0.96, 1.75).

Conclusion: Advanced age, male gender, nodal involvement, and unilateral tumor location were poor prognostic factors.

Key words: lung cancer, multiple, prognosis, surgery, survival

introduction

Surgery alone is a potentially curative treatment of early-stage, nonsmall-cell lung cancer (NSCLC). However, as the stage of NSCLC advances, the risk of metastasis increases, and the efficacy of surgery, as a single modality, decreases. Determining appropriate treatment of patients with isolated NSCLC is generally straightforward. Nevertheless, when there are multiple cancers in two or more lobes, this can be problematic. In the absence of extrathoracic metastasis, these cancers may develop from independent primaries or they may represent metastatic foci. In the former scenario, surgery may be helpful; however, in the latter scenario, surgery may not adequately address the underlying systemic disease. Available data indicate that this problem is not common. For example, data from 6596 patients with 'metastatic' NSCLC submitted to the American Joint Commission for Cancer Staging in 1990–2000 for M1 description indicated that 1106 patients (17%) had metastatic disease solely on the basis of unilateral multiple lobe cancers and 369 (6%) on the basis of bilateral cancers [1]. Regardless of their biological development, these cancers seem to portend a poor prognosis overall. Several early studies have reported no long-term survivors after surgery [2–6]. As a result, the vast majority of such patients do not receive curative surgical treatment [7].

Nevertheless, attempts have been made to identify multiple independent primary cancers as a target for surgical intervention, on the premise that surgery is a curative

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treatment of early-stage cancers. In 1975, Martini and Melamed introduced the first of such criteria [8]. Other authors have since built upon this [9–11], though a few common rules can be summarized. The first relies on temporality: cancers with lag time >2–4 years are considered independent primaries. Unfortunately, this is not helpful for patients with synchronous cancers. The second rule relies on histological similarity: cancers with similar histology are metastatic, if there is carcinoma in lymphatics common to both (i.e. mediastinal (N2) lymph node involvement). However, this rule requires the precise knowledge about all histological features of the cancers including the presence of N2 involvement, making it impractical for use when surgery has not taken place. Besides, the rule is not informative for patients with N1 disease. In addition to these rules, the current AJCC staging relies on location [1]: cancers with bilateral location are metastatic. However, long-term survivors have been reported after surgical resection among patients with bilateral cancers [12, 13].

As there appears to be a room for improvement in the prognostication of patients with synchronous multiple lung cancers, in this article we systematically review the literature specific to this patient population for their survival following surgery. As available observational studies may have inadequate statistical power or adjustment for the differences in baseline characteristics, we perform a pooled analysis, using individual patient data adjusting for multiple covariates simultaneously, to identify the independent prognostic factors for survival after surgery.

methods

search strategy

An institutional Scientific Review Committee has determined this study as nonhuman subject research and exempted it from Institutional Review Board. Electronic searches were carried out in Medline, PubMed, and Web of Sciences databases from January 1990 to October 2011 with a restriction to publications in English. To achieve the maximum sensitivity of the search strategy and identify all publications relevant to surgical resection of multiple lung cancers, we used appropriate free text and thesaurus terms including 'multiple' or 'second' and the medical subject headings of 'lung neoplasm', 'surgical procedures, operative', and 'general surgery'. The reference list of all retrieved articles was reviewed for further identification of potentially relevant publications. In addition, abstracts from the American Society of Clinical Oncology and European Society of Medical Oncology were also searched for potential studies.

study selection

Eligible patients were those with multiple synchronous NSCLC located in multiple lobes resected with curative intent. Patients who had satellite nodules or cancers located in one lobe were included for analysis, providing that they also had cancers located in multiple lobes. Synchronous cancers were defined as those discovered within a 24-month time period, including those found intraoperatively. To reduce reporting bias, studies reporting on the survival outcome of at least 10 eligible patients were included. Excluded studies were those solely reporting patients who had resections for benign nodules, only one of the multiple cancers were resected, distant metastatic disease, multiple cancers in only one lobe, or metachronous cancers. Reports focusing on bronchioloalveolar carcinomas (BAC) in all lesions or carcinoid tumors were also excluded. Corresponding authors of eligible studies were contacted to obtain individual patient database for analysis.

data management and quality assessment

Databases were as supplied by collaborators. In two databases, time variables were available in month to maintain patient confidentiality. Two investigators (one clinical, T.T., and one nonclinical, W.J.F.) reviewed each included article. Data retrieved from each report included publication details, patient characteristics, and outcome measures. The data extracted were entered into the Cochrane Collaboration software. Histological difference was based on major histological type (i.e. adenocarcinoma versus squamous cell carcinoma). Patients with cancers both in ipsilateral multiple lobes and contralateral lung were analyzed together with the group of patients who had solely bilateral cancers without ipsilateral involvement of multiple lobes. Staging information was pathological. The quality of study reporting was assessed based on the selected key elements, which may affect the results and interpretations of our review [14]. Reporting was conformed to the PRISMA statement [15].

statistical analysis

The main outcome was overall survival, defined as an interval between the first resection and the date of death or last follow-up for censored cases. To account for a possible heterogeneity among studies, a pooled analysis using the technique of meta-analysis to pool effect sizes was conducted [16]. The summary measure was a hazard ratio (HR). To calculate the adjusted HR in each study, multivariable Cox proportional hazard models were fitted for each study incorporating age, gender, tumor side, histological similarity, nodal stage, and having pneumonectomy. The log-rank observed and expected number of events and associated variances were calculated from adjusted HR in each study [17]. The overall pooled HR and their 95% confidence intervals (CI) were then calculated using a fixed effects model. Chi-square heterogeneity tests were carried out. We calculated I^2 statistics expressing the proportion of variability in the results attributable to heterogeneity rather than sampling error, with I^2 statistic <25% indicating low heterogeneity, 25%–50% moderate heterogeneity and >50% high heterogeneity [18]. When moderate heterogeneity was observed, random effects model was used to pool HR [19]. All P values were considered significant at the level <0.05. All analyses were carried out using SAS version 9.3 (Cary, NC) and Comprehensive Meta-Analysis from Statistical Solutions (Saugus, MA).

results

study and patient characteristics

A total of 2805 titles were identified through electronic database searches and screening of reference lists (Figure 1). After excluding irrelevant reports, 114 publications were retrieved for detailed evaluation. There were no duplicate studies. Of these, 10 studies were eligible and individual patient data were made available from six studies. All studies were retrospective, published during 2008–2011, including patients receiving surgery during 1983–2009. Two of these studies also included patients with metachronous cancers or cancers located in one lobe and data from only 467 eligible patients were included for analysis from a total of 661 patients originally reported (Table 1).

Overall, the patient median age was 69 years (range 42–86 years) and 54% were male. Tumor characteristics showed N0 325 patients (70%), N1 67 (14%), and N2 75 (16%); unilateral

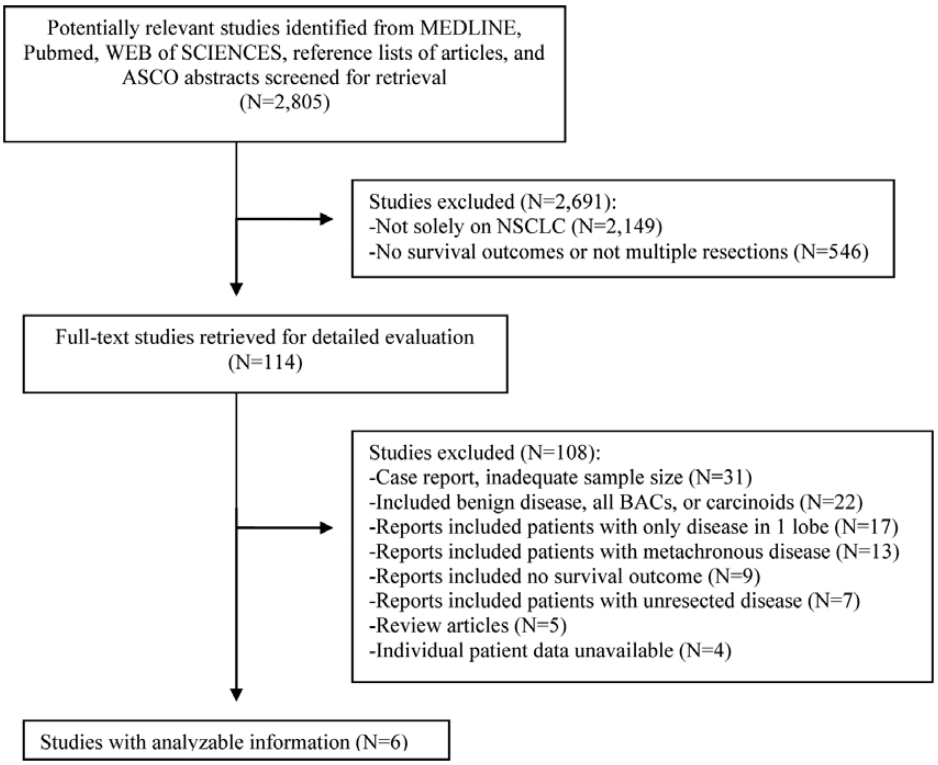

Figure 1. Flow chart of study selection.

Table 1. Characteristics of analyzed patients

First authors, publication year (reference)	Riquet, 2008 [25]	Voltolini, 2010 [22]	Finley, 2010 [11]	Tanvetyanon, 2010 [21]	Fabian, 2011 [23]	Kocaturk, 2011 [24]
Treatment year	1983–2005	1990–2007	1995–2006	1997–2008	1996–2009	2001–2008
Total number of patients	234[a]	43	175[b]	116	67	26
Total number of analyzed patients	61	43	154	116	67	26
Male gender (%)	77	95	41	41	45	100
Age (%)						
<55	16	9	8	5	6	35
55–65	46	28	24	20	19	38
65–75	28	54	47	49	42	23
>75	10	9	21	26	33	4
N stage (%)						
N0	49	58	71	81	82	42
N1	10	19	15	7	10	58
N2	41	23	14	12	7	0
Tumor location (%)						
Unilateral	84	35	52	49	34	54
Bilateral	16	65	48	51	66	46
Histology (%)						
Similar	56	63	82	68	56	65
Different	44	37	18	32	54	35
Pneumonectomy	43	14	3	9	0	42

[a]Original report included 234 patients; data from 61 patients with synchronous cancers in multiple lobes presented in this table.
[b]Original report included 175 patients; data from 154 patients with cancers in multiple lobes presented in this table.

tumors 240 patients (51%) and bilateral tumors 227 patients (49%); similar histology 314 patients (67%) and different histology 153 (33%). Treatment characteristics showed pneumonectomy was carried out in 57 patients (12%). The duration between the first and the final operation was >6 months in 55 patients (12%).

quality of study reporting

Although no uniform agreement exists regarding the instrument to assess the quality of study reporting, for an observational study, it is generally recommended that relevant details regarding participant selection and measurement of key variables be assessed [14, 20]. We considered specific reporting issues, which, if inadequate, could compromise the results of our analysis. For our review purpose, we evaluated the studies for an explicit reporting of (1) method to exclude patients with an extrathoracic disease, (2) whether BAC was distinguished from an invasive adenocarcinoma, (3) method of mediastinal staging, (4) number of sublobar resections, (5) number of patients with positive surgical margins or receiving adjuvant therapy, and (6) method of follow-up or last follow-up date.

Overall, we found the quality of reporting in these studies to be acceptable for data synthesis. All but one study explicitly specified the methodology used to exclude patients with extrathoracic metastasis. The use of preoperative Positron Emission Tomography scan in selected patients was described in five of six studies. However, most did not specify the number of patients who underwent the scan. The majority of patients with N2 disease were those with microscopic N2. Of six studies, three indicated an exclusion from surgery for patients with known N2 [11], bulky or multistation N2 [21], >1 cm N2 [22]. One study excluded N2 patients from analysis if the histology was similar [23]. One study excluded all N2 patients from analysis [24] and finally, the other study did not specify N2 policy [25].

surgery and outcomes

Surgical characteristics and outcomes are summarized (Table 2). These results are not exclusively from eligible patients. Sublobar resections occurred frequently, ranging from 16% to 78% of patients. The reported postoperative mortality rate ranged from 1.2% to 7.6% of patients. At the time of reporting, 248 patients have died. The median overall survival was 52.0 months (95% CI 45.6–63.7). The likelihood of death within 30 days from surgery was 1.9%. Most patients had two cancers; however, 35 patients (7%) had three cancers, 12 patients (3%) had four cancers, and five (1%) patients had greater than four cancer foci.

prognostic factors for survival

We pooled the adjusted HRs obtained from each study, taking into account gender, age, pneumonectomy, nodal stage, histological similarity, and tumor location. Gender, age, nodal stage, and tumor location were significant predictors of survival. Female gender was associated with a decreased mortality: HR 0.61 (95% CI 0.45–0.82), $P = 0.001$. Increased age (per year) was associated with increased mortality: HR 1.02 (95% CI 1.01–1.04), $P = 0.006$. N1 or N2 stage, when compared with N0, was associated with increased mortality: HR 1.68 (95% CI 1.12–2.51), $P = 0.01$, and HR 1.94 (95% CI 1.33–2.82), $P = 0.005$, respectively. Bilateral tumor location was associated with a decreased mortality: HR 0.69 (95% CI 0.50–0.94), $P = 0.02$. There was a trend toward increased mortality risk among patients with different histology: HR 1.29 (95% CI 0.96–1.75), $P = 0.09$. Moderate heterogeneity was observed on gender and tumor location analyses. However, when re-examined using a random effects model, female gender and bilateral tumor location remained significant favorable predictors of survival: HR 0.63 (95% CI 0.43–0.93), $P = 0.02$ and HR 0.62 (95% CI 0.38–0.99), $P = 0.048$ respectively. We carried out a subgroup analysis based on data obtained from patients who completed all their surgical operations within a 6-month period. In this subgroup, there were 412 patients with a

Table 2. Characteristics of surgery and adjuvant treatments

First authors, publication year (reference)	Riquet, 2008 [25]	Voltolini, 2010 [22]	Finley, 2010 [11]	Tanvetyanon, 2010 [21]	Fabian, 2011 [23]	Kocaturk, 2011 [24]
Total number of patients originally reported	118[a]	43	175	116	67	26
Patients with ≥2 surgical procedures	NR	65.1	40.7	58.6	80.6	46.2
Patients with ≥3 cancers (%)	NR	14.0	28.6	7.8	4.5	7.7
Patients with at least one sublobar resection (%)	16.1	65.1	54.3	78.4	62.7	38.5
Patients with multistaged resections (%)	NR	65.1	41.7	58.6	67.1	46.1
Pneumonectomy (%)	34.7	13.9	2.9	8.6	1.5	38.5
Adjuvant/neoadjuvant therapy (%)						
Chemotherapy	NR	34.9	9.7	20.7	25.0	NR
Radiotherapy	NR	10.0	4.6	14.7	3.0	NR
Any of the above	41.5	39.5	14.3	31.0	26.9	NR
Operative mortality rate (%)	5.1	6.9	1.2	4.3	2.9	7.6
Most frequent complications (%)	NR	Air leak (13.9%)	NR	Arrhythmia (8.6%), infection (8.6%)	NR	NR

NR, data not reported.

[a]Original study reported on 234 patients; data specific to 118 patients with multiple synchronous cancers presented in this table.

median survival of 50.7 months (95% CI 64.4–80.0). We found similar trends as observed in the whole group.

To illustrate the impact of these prognostic factors, we created a Kaplan–Meier estimate of survival using a pooled dataset from six studies. Patients were categorized into two groups based on the presence of risk factors (gender, age, nodal stage, and tumor location). For the age variable, we empirically chose to use a cutoff at <70 versus ≥70 years because the median age of the patients was 69 years. We found that patients with no risk factor ($N = 43$) had a considerably better survival than those with ≥1 adverse risk factor ($N = 424$). The estimated 5-year survival rate was 82% (95% CI 70–96) among those with risk factors absent versus 43% (95% CI 38–48) among those with risk factor(s) present (Figure 2).

discussion

In this study of synchronous lung cancers located in multiple lobes, we found that male gender, advanced age, higher nodal stages, and unilateral tumor location were adverse predictors of survival after surgical resection. The strongest predictor was N2 (1.94 times higher than N0), followed by N1 (1.68 times higher than N0), male gender (1.64 times higher than female), unilateral tumor location (1.45 times higher than bilateral), and age (~1.40 times higher every 20-year increase because each year adds 0.02 to the number), respectively. Pneumonectomy, previously suggested by some authors as a poor prognostic factor [12], was not found to affect survival. Histological similarity, also suggested by some as a poor prognostic factor [26], was not associated with poor survival. In fact, there was a trend toward improved survival among patients with similar histology.

In line with our observations, other studies, albeit with somewhat different patient inclusion criteria, have previously suggested a more favorable survival among patients with bilateral cancers [12] and similar histology [27, 28] than their counterparts. It is hypothetically possible that patients with bilateral cancers or similar histology may include a significant number of those with mixed adenocarcinoma with BAC component. BAC, now known as adenocarcinoma *in situ* in the latest WHO classification, tends to occur among young

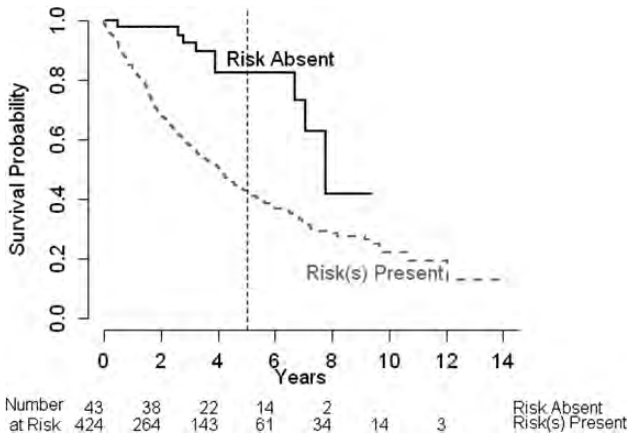

Figure 2. Kaplan–Meier survival curves by the presence of risk factors.

women, may manifest multifocally or bilaterally, and can run an indolent course [29, 30]. The higher the proportion of BAC component exists in a given invasive adenocarcinoma, the better the prognosis [31]. Although we excluded studies focusing on pure BAC, we were unable to exclude studies containing invasive adenocarcinoma with BAC feature. Alternatively, the survival among patients with bilateral disease may be favorable simply because such patients are more likely to be those with true multiple primary cancers. Given the distance between cancers, patients with bilateral cancers, which truly arise from hematogenous spread will likely have obvious extrathoracic metastases, rendering them not a surgical candidate. Finally, it is also possible that patients with bilateral cancers are generally more select group than those with unilateral cancers, given the prevailing notion that bilateral cancers confer a poorer prognosis than unilateral cancers.

The observed favorable prognosis among patients with bilateral cancers seems to be somewhat discordant with the seventh edition of AJCC staging system, which classifies bilateral cancers as stage IV (M1a), but classifies unilateral cancers in multiple lobes as stage III (T4) [1]. This discordance probably stems from the fact that that only 2% of patients with bilateral cancers who formed the basis of AJCC staging recommendation actually had surgery, while in this review, all patients had surgery. Bilateral cancers, in contrast with unilateral cancers, more frequently require staged thoracotomies. As this review included only patients who actually had resections of their bilateral cancers, it is possible that some patients who, for whatever reasons, did not undergo the second thoracotomy would not be included. If the survival among such omitted patients were poorer than those included in the analysis, the omission could result in a bias favoring the group of bilateral cancers, when compared with the group of unilateral cancers.

The strength of this report includes the fact that it contains the largest number of analyzed patients with multiple synchronous lung cancers and it is the first pooled analysis on this topic. Nevertheless, there are a number of weaknesses. First, the report contains highly select patients treated at high-volume centers. Therefore, the favorable survival outcome may not be generalizable to all patient population. Nonetheless, we believe that the prognostic factors derived from this dataset should still be useful for clinical decision making. Second, variables such as lung function, tumor size, adjuvant therapy, and comorbidity were not included in our analysis. However, among a subgroup of 270 patients with available data on tumor size and adjuvant therapy, we found no substantive difference in the variables when stratified by the significant prognostic factors. Third, unlike other variables, histological similarity is susceptible to nondifferential misclassification, potentially biasing the effect estimate to the null. Of the six studies reviewed, only one study [11] specified the pathological criteria for NSCLC classification and required the availability of pathological specimens for re-reading. Nevertheless, the null result is probably more in keeping with usual clinical practice, when misclassification is probably more frequent than what observed in this review. Fourth, some authors define synchronous cancers as those discovered simultaneously. Nevertheless, the 2-year definition was chosen for this review

in accord with the majority of literature based on the fact that some small lesions, though initially present, may be beyond radiographic resolution or simply undocumented. Finally, it is unclear whether other treatment approaches including stereotactic body radiation or erlotinib [32] will yield a better result than surgical approach.

Despite these limitations, a number of practical implications can be derived. First, surgery is a curative treatment option for patients with synchronous lung cancers in multiple lobes, even when it is unknown whether the cancers are multiple primary lung cancers or metastatic disease, and even when the cancers are bilateral or bear similar histology. Therefore, if such patient appears to be a good operative candidate, we believe that it is inappropriate to simply offer palliative chemotherapy without first seeking a surgical consultation. Second, AJCC staging appears to largely overstage patients with multiple lung cancers who underwent curative resections, especially those without adverse prognostic factors mentioned above. Finally, patients with N2 (mostly microscopic N2) or N1 have a nearly similar elevated risk of death. Although long-term survival among patients with N1 or N2 was observed in our review, these patients required additional therapies after surgery. Therefore, the presence of nodal involvement (either N1 or N2), especially along with other poor prognostic predictors, indicates an aggressive clinical course and consideration should be first given to other available curative treatment options.

In summary, among select patients who underwent surgery for synchronous multiple lung cancers in multiple lobes, several simple clinical characteristics can serve as survival predictors. The absence of adverse prognostic factors portends an excellent long-term prognosis with over 80% estimated survival rate at 5 years. This exploratory meta-analysis of published databases may be useful for hypothesis generating and planning for future prospective studies.

disclosure

The authors have declared no conflicts of interest.

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