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Review

Outcomes of lung cancers manifesting as nonsolid nodules

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ABSTRACT

This is a comprehensive review and re-analysis of available literature to assess the outcome of lung cancer presenting as nonsolid nodules (NSNs), a more indolent form of cancer. PubMed and EMBASE were searched for articles reporting on CT-detected lung cancers manifesting as NSNs published in English on or before July 17, 2015. Only studies including clinicopathologic data, lung cancer-specific survival, or overall survival were included. Data extraction was performed by three independent reviewers using prespecified criteria. Twenty-four articles from 5 countries met criteria and they included 704 subjects with 712 lung cancers manifesting as NSNs. Each article reported from 2 to 100 lung cancer cases with a median follow up of 18–51 months. All NSNs were Stage I adenocarcinoma without pathologic nodal involvement upon resection, except for one case in which the NSN progressed to become part-solid nodule after 6 years of follow-up. The five-year lung cancer-specific survival rate was 100%. These findings suggest an indolent course for lung cancers manifesting as NSNs.

1. Introduction

With advances in computed tomography(CT) scanner technology, nonsolid nodules (NSNs), which are nodules that have no solid components other than blood vessels, are being identified with increasing frequency on chest CT scans performed in programs of CT screening for lung cancer as well as for other indications [1]. NSNs have also been described as *ground-glass opacities (GGOs), pure ground-glass opacities (pGGOs), or as pure ground-glass nodules (pGGNs).*

Studies have reported excellent surgical outcomes for lung cancers manifesting as NSNs when treated [2], which raised the possibility that these outcomes were not only the result of potentially curative surgery, but also that these lung cancers might have an indolent course even in the absence of treatment [1,3–5]. As a result, concerns have been raised about the possibility that resection may represent 'overtreatment' [1,6]. However, most of these studies are based on a small number of patients with limited follow-up [7].

Combined with rapid advances in CT technology, and the wide spread use of CT for lung cancer screening [8,9], the frequency of detecting NSNs will significantly increase and further knowledge as to the best approach to manage them is urgently needed. A review of available literature is needed to confirm the indolent nature of these cancers as well as to ensure that no harm is caused to the patient by delaying a potentially lifesaving opportunity to resect a cancer before it progresses to higher stage disease.

2. Methods

2.1. Data sources and searches

The PubMed/MEDLINE and EMBASE databases were searched for all studies and clinical trials on CT-detected lung cancers published in English on or before July 17, 2015. Search strategies are listed in Appendix A. Furthermore, reference lists of all identified relevant articles and important reviews in this topic were manually searched.

Abbreviations: AIS, Adenocarcinoma-in-situ; CT, Computed tomography; GGO, Ground-glass opacities; IQR, Interquartile range; LN, Lymph node; MLND, Mediastinal lymph node dissection; NSNs, Nonsolid nodules; MIA, Minimally invasive adenocarcinoma; PGGO, Pure ground-glass opacities; VDT, Volume doubling time.

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2.2. Study selection

Titles and abstracts (and in ambiguous cases, full text) of the articles were reviewed by two independent reviewers (RY, KT) for eligibility of studies. Inclusion criteria were: cohort, controlled or randomized studies performed in humans; lung cancers manifesting as NSNs using CT; and studies that reported on at least one of the following outcomes of interest: (i) lung cancer-specific survival, (ii) overall survival, (iii) lymph node involvement, (iv) invasion, (v) clinical/pathologic stage, or (vi) recurrence. Studies that did not meet the inclusion criteria and non-English published studies were excluded. Also excluded were those studies that included GGO with less than a 100% ground glass component(part-solid) in which we were unable to determine the outcomes for those cases with "pGGO."

2.3. Data extraction

Data were extracted independently by three reviewers(RY, AW, and KT). In cases of discord, final decision was decided by a fourth reviewer(DY or CH). When available, information on first author, country of participants and year of the study were extracted. Other study characteristics collected were the number of lung cancer cases manifesting as NSNs, initial size, size at time of diagnosis for nonsolid cancers, type of surgery, lung cancer histology, stage of cancer at diagnosis(clinical/pathological), number of cases with mediastinal lymph node dissection(MLND)/sampling, positive lymph node(LN) metastasis, length of post-operative hospital stay, recurrence, overall and lung cancer-specific, and duration of follow-up.

2.4. Pathologic classification

For the review, the updated classification for adenocarcinoma proposed by Travis et al. [10,11] was used, in which the term "bronchioloalveolar features" was replaced by the term "lepidic." The updated description used adenocarcinoma-in-situ(AIS) to replace *adenocarcinoma with bronchioloalveolar features*, which by definition has no evidence of invasion. Minimally invasive adenocarcinoma(MIA) was used for cases of invasive adenocarcinoma with 90–99% lepidic subtype(formerly bronchioloalveoalar features) with less than 5 mm of invasion. For invasive adenocarcinomas, the subtype was classified by predominant component: lepidic, acinar, papillary, micropapillary, or solid. Summary of these changes has been previously reported [12,13].

2.5. Data synthesis and analysis

Frequencies and descriptive statistics were obtained for all variables. A resampling method [14] with 1000 iterations was used for estimating the sampling distribution of the percentage of noninvasive adenocarcinoma. Such resampling provides for more robust estimates and the summary statistics from the 1000 samples were given.

2.6. Bias

All 24 studies included in this review were retrospective observational studies. As anticipated, there are no published randomized clinical trials in which the effects of surgery on the long term lung cancer survival among cancers manifesting as NSNs were studied. Since all included studies are observational and consisted of mostly resected cases, selection bias may have been introduced when deciding which patients should undergo surgery.

It is possible that management of NSNs may be different among different countries, institutions and surgeons and this may have played a role in the decision to perform surgery. Among the 24 studies, 22 [2,6,7,15–33] included only institutions in Asia (618 of 704 patients), one study included institutions in 8 countries, predominantly in the United States, but also in Europe, Japan and China [1] (84 of 704 patients) and one study [34] included 2 of the 704 cases from Germany. In 3 studies [16,18,25] accounting for a total of 48(7%) resected cases, only patients who underwent limited resection were included.

Average tumor size of the cases was relatively small, ranging between 7.9 mm to 16.6 mm. Tumor size was one of the inclusion criteria in some of the studies; inclusion was restricted to subcentimeter(< = 1 cm) tumors in 3 studies [2,17,33] and to ≤2 cm in 4 studies [21,22,30,35], for a total of 80(11%) and 148(21%) resected cases respectively.

No standard measuring methods or CT acquisition parameters were used in the 24 included studies; the time from the initial identification of the NSN to the time of resection was not reported. Of the 18 studies (495 cases) in which the median follow-up time after surgery was reported, median follow-up time ranged from 12 to 78 months of which 12 studies (339 or 68% of total cases) had a median follow up of more than 3 years, and 2 studies (134 or 28% of total cases) had more than 5 years follow-up. In 2 studies, only persistent NSNs after ≥2 years of follow-up after the initial identification were included (45 or 9% of total cases).

2.7. Confounders

The year of study conduct may be important as CT scanner and surgical techniques may have changed over time. However, lung cancer survival was consistently at 100% in the 24 included studies without any changes over time according to year of publication. Our review confirms the excess of females and non-smokers as has been noted in prior studies [2].

3. Results

The PubMed/MEDLINE and EMBASE search identified 775 potential articles (Fig. 1). Studies were selected according to the inclusion and exclusion criteria. Eighty studies were obtained from this search and six additional publications were identified by a manual search of the bibliographies of the relevant articles. A total of 30 articles reporting on 24 unique studies were included in this review [1,2,6,7,15–34,36–41].

Table 1 summarizes the 24 studies conducted from 1991 to 2014. Most studies were conducted in China, Taiwan, Korea, or Japan, with one multi-institutional study in the USA and one in Germany. A total of 704 patients with 712 lung cancers manifesting as NSNs were reported. All 712 were resected except two: one patient declined surgery due to the presence of lesions in all lobes [15] and one patient chose radiation therapy instead [1]. The average age of participants ranged from 53 to 68. The number of participants with lung cancer manifesting as NSNs in each study ranged from 2 to 100, with median follow-up after surgery ranged from 18 to 78 months. Among the 24 included studies, CT acquisition parameters were reported in 18 studies. CT images were being acquired at 2.5 mm or less in 5 studies, 2.0 mm or less in 7, and 1.0 mm or less in 6. Of the 24 studies, 2 studies included only screen-detected NSNs [1,6], both screen-detected and incidental detected NSNs in 3 [15,16,31], and the remaining 19 did not specify but it is presumed that non-screen detected nodules were included. Among the studies in which the type of resection was reported for all resected lung cancers, the extent of surgery varied by country of study. The frequency of sublobar resection was 63–100% in Japanese studies but lower in Korea and China (27–41%). The only multi-institutional study which included institutions in the United