Lung Cancer 88 (2015) 174–180

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Survival of a surgical series of lung cancer patients with synchronous multiple ground-glass opacities, and the management of their residual lesions☆

Yoshihisa Shimada[a,*], Hisashi Saji[c], Keishi Otani[a], Sachio Maehara[a], Junichi Maeda[a], Koichi Yoshida[a], Yasufumi Kato[a], Masaru Hagiwara[a], Masatoshi Kakihana[a], Naohiro Kajiwara[a], Tatsuo Ohira[a], Soichi Akata[b], Norihiko Ikeda[a]

[a] First Department of Surgery, Tokyo Medical University Hospital, Tokyo, Japan
[b] Department of Radiology, Tokyo Medical University Hospital, Tokyo, Japan
[c] Department of Chest Surgery, St. Marianna University School of Medicine, Yokohama, Japan

ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form 4 February 2015
Accepted 23 February 2015

Keywords:
Non-small cell lung cancer
Multiple lung cancer
Ground-glass opacity
Surgical resection

ABSTRACT

Objectives: We reviewed the medical record of a series of patients with synchronous multiple lung cancers (SMLC), in an attempt to identify the optimal treatment strategy for multiple ground-glass opacities (GGOs).

Materials and methods: From 2004 to 2010, 1223 patients underwent complete resection of non-small cell lung cancer. Among these, there were 67 patients (5.5%) with SMLC with at least 1 of the nodules showing GGO appearance. SMLC was divided into the main cancer (MC) which was a main target based on its tumor size or radiological invasiveness and sub-nodules. According to consolidation/tumor ratio (CTR) on thin-section computed tomography, 67 cases were classified into GG-group (MC showing GGO-dominant lesion; CTR $\leq$ 0.5) and GS-group (MC showing solid-dominant lesion; CTR > 0.5).

Results: There were 24 patients in the GG-group (36%) and 43 patients in the GS-group (64%). Surgical resections included 11 sublobar resections (SLs), 32 lobectomies, 19 lobectomy + SLs, and 4 bilobectomies. There were 39 patients with a total of 118 unresected GGOs after the initial surgery. Among them, the frequency of growth was 8% on a per-nodule basis with the median tumor doubling time of 1373 days, and new GGOs emerged in 15 patients (23%). Multivariate analysis demonstrated that larger size of MC and the GS-group was associated with poor prognosis, whereas growth of the residual GGOs, the development of new GGOs, or whether or not all GGOs were treated did not affect survival. The 5-year OS proportions were 95.8% for the GG-group and 68.0% for the GS-group ($p = 0.009$), and 92.4% for a MC of $\leq$25 mm and 53.6% for a MC of >25 mm ($p = 0.008$).

Conclusion: Survival of patients with multifocal GGOs is strongly affected by radiological findings of the MC. Strict surgical control for MC could be most important.

1. Introduction

The widespread use of high-resolution computed tomography (CT) in daily practice and screening has contributed to the frequent detection of ground-glass opacities (GGOs) in asymptomatic patients [1,2]. GGO is defined as a hazy area of increased attenuation in the lung, with preservation of the bronchial and vascular margins, and can be caused by various diseases, such as infections, interstitial diseases, acute alveolar diseases, and neoplasms [3]. GGO lesions are often detected as multiple lesions, and the incidence of multiple primary lung cancers with GGOs has recently increased [4,5].

Abbreviations: CT, computed tomography; GGO, ground-glass opacity; MC, main cancer; SN, sub-nodule; CTR, consolidation/tumor ratio; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; SBRT, stereotactic body radiation therapy; IQR, the interquartile range.

☆ *Grant support*: This study was supported by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (26861130), and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

* Corresponding author at: First Department of Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. Tel.: +81 03 3342 6111; fax: +81 03 3342 6203.
E-mail address: zenkyu@za3.so-net.ne.jp (Y. Shimada).

http://dx.doi.org/10.1016/j.lungcan.2015.02.016
0169-5002/

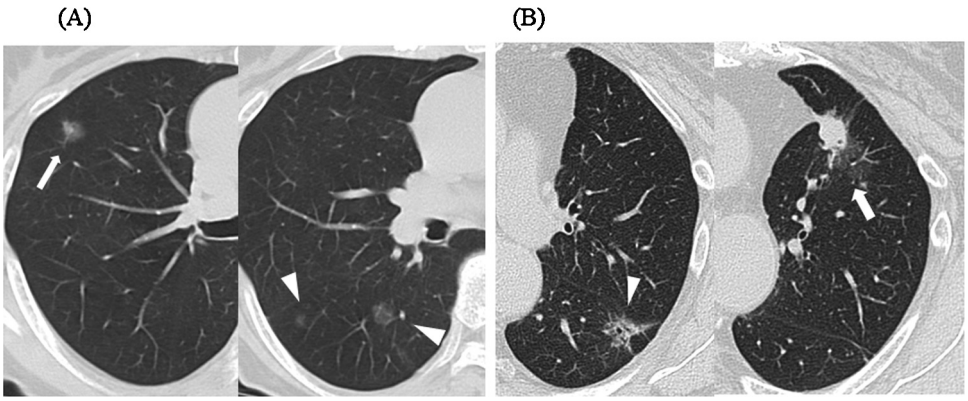

Fig. 1. Typical CT images of synchronous multiple lung lesions. (A) A 71-year-old female patient from the GG-group; the arrow shows the 11-mm MC in the right segment 3 area, and the two arrowheads show a 9-mm and a 5 mm SN in the right segment 6 area, respectively. (B) A 80-year-old female patient of the GS-group; the arrow shows the 41-mm MC in the left segment 3 area, and the arrowhead shows a 23-mm SN in the left segment 6 area.

The detection of synchronous multiple lung nodules may cause the clinical dilemma of how these lesions should be managed. The distinction has important therapeutic and prognostic implications. Although surgical approaches for such multiple lesions depend on their anatomical location, size, and number, as well as the patient's age, and pulmonary function, the decision usually depends on the surgeon's judgment; no standard criteria have been established for the selection of the lesions to be treated, nor the method of management of the residual nodules in cases of synchronous multifocal GGOs. In this study, we retrospectively reviewed the records of a surgical series of lung cancer patients with synchronous multiple lung lesions, proven or suspect for lung cancer, particularly multifocal GGOs, in an attempt to identify the optimal treatment strategy and the management method for the residual and new lesions.

2. Patients and methods

2.1. Patients

From January 2004 to December 2010, a total of 1223 patients underwent complete resection without any preoperative induction therapy for non-small cell lung cancer at our hospital. Among them, 85 patients had either synchronous multiple primary lung cancer or underwent main tumor resection with at least 1 other lesion suspected of lung cancer on preoperative CT scans. Of these, 67 patients (5.5%) who possessed at least one lung lesion showing an area of GGO were included in the study. In the patients who underwent resection for all lung tumors, they were diagnosed as multiple lung cancer with GGO component due to their pathological and clinical characteristics based on the modified Martini and Melamed criteria, the American College of Chest Physicians guidelines, and the theories of the multiclonality of multifocal lepidic-type adenocarcinoma [4,6,7]. The stages of the tumors were determined in accordance with the 7th Edition of the TNM Classification for Lung and Pleural Tumors [8]. This retrospective study was evaluated by the Institutional Review Board of Tokyo Medical University and granted exemption from the requirement for informed consent.

2.2. Radiological evaluation of synchronous multiple lung lesions

CT scans were performed by using a 64-channel MDCT (Light Speed VCT, GE Medical Systems, Milwaukee, WI, USA) with a section thickness of 1.25 mm. Each CT image was acquired within 1 breath hold of about 5 s, after a delay of 70 s during which the contrast media injection took effect.

When collecting and analyzing our data, we firstly divided synchronous multiple lung GGO lesions into two lesions according to the preoperative CT findings; the main cancer (MC) and subnodules (SNs). MC was defined as the main lung cancer to be surgically resected, from its tumor size or radiological invasiveness, and SNs were any other lung lesions.

According to the radiological findings on thin-section CT scan, we examined the ratio of maximum diameter of consolidation to the maximum tumor diameter from the lung window (CTR). The cases were classified into two groups: GG-group and GS-group. The GG-group denotes their MC showing GGO-dominant appearance (CTR $\leq$ 0.5) and the GS-group shows their MC showing solid-dominant appearance (CTR > 0.5), respectively. The radiological criteria of a CTR 0.5 as a cut-off in this study depends on results of several published studies [9–11]. Typical CT findings of patients in the GG-group and the GS-group are shown in Fig. 1A and B, respectively.

2.3. Treatment strategy and postoperative surveillance

In patients with multiple lung lesions, the surgical procedure was determined according to site of lesion, CT findings, estimated postoperative respiratory function, and the presence or absence of preoperative comorbidities. Our basic treatment strategy for synchronous multiple lung lesions was as follows (Supplement Fig. 1): (1) when tumors were in an ipsilateral chest, we tried to resected all lesions larger than 10 mm or radiographical solid-dominant lesions by single-stage surgical treatment. However, for SNs smaller than 10 mm or radiographical GGO-dominant lesions with slow growth, if the extent of the resection was expected to be greater than sublober resection because of the central location or if there were multiple lesions scattered throughout multiple lobes, we decided to perform strict surgical resection of MC and easily accessible SNs by limited resection. (2) When tumors were in contralateral lesions, two-stage surgical treatment was commonly performed. (3) As our strategy throughout the postoperative follow-up period, we performed surgical resection on SNs with a diameter of larger than 10 mm, or with an emerging solid portion. Unless patients were capable of undergoing surgical resection in estimated postoperative respiratory function, we decided not to resect such lesions and instead select SBRT or continuous monitoring of the residual lesions (Supplement Fig. 2).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.02.016.