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ORIGINAL ARTICLE

Radiotherapy for oligometastatic tumor improved the prognosis of patients with non-small cell lung cancer (NSCLC)

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Non-small cell lung cancer; oligometastasis; radiotherapy.

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Abstract

Background: This study was conducted to investigate if radiotherapy improved the overall survival (OS) of patients with oligometastatic non-small cell lung cancer (NSCLC).

Methods: From January 2012 to August 2015, 323 NSCLC patients with distant metastasis were administered radiotherapy. Ninety-five patients with oligometastatic NSCLC who were sensitive to the initial chemotherapy were treated with radiotherapy for the residual lesions. Initial treatment consisted of four to six cycles of induction chemotherapy. If the patients responded to the initial treatment without developing new metastases, the residual sites were radiated at a total dose of 56–66 Gy, including the primary and metastatic sites. OS, progression-free survival, and sites of progression were assessed. The Kaplan–Meier method was used to estimate the OS and progression-free survival probabilities.

Results: The median survival of the whole cohort was 15 months (95% confidence interval 6–40) and the median time to progression was 11 months (95% confidence interval 4–24). Sixty-seven patients had died by the end of follow-up. The one-year and two-year OS rates were 58% and 23%, respectively. Patients progressed either with brain (n = 14), bone (n = 11), lung (n = 10), liver (n = 7), adrenal gland (n = 5), or seven other sites of metastases (n = 3). Acute grade III esophageal toxicity was observed in 17 patients (18%) and grade III pulmonary toxicity in seven patients (7%).

Conclusion: Oligometastatic non-progressive NSCLC patients may benefit from aggressive radiotherapy to the residual lesions with acceptable toxicity after systemic chemotherapy.

Introduction

Lung cancer (LC) is the most common malignancy and the leading cause of cancer-related mortality worldwide. Non small cell lung cancer (NSCLC) is the major type of LC, accounting for approximately 85% of all cases, and approximately 30% of patients present with metastatic disease at the time of diagnosis.[1] Palliative supportive systemic chemotherapy (ChT) is recommended as the standard therapy for patients with metastatic NSCLC, which provides a minimal chance of long-term survival, with median survival of 8–11 months.[2] However, not all patients with metastasis have a poor prognosis; for example, colorectal cancer patients improve after resection of liver metastasis. In the 1990s, Hellman and Weichselbaum reported the existence of an intermediate "oligometastatic state" in which tumors develop sites of distant metastasis in a single or limited number of organs as a function of the underlying biology of tumor cells and the unique receptiveness of distant organ sites.[3] The oligometastatic state is distinct among those with metastatic disease and consists of patients with metastases limited in number and location, representing an intermediate state between locally confined and widely metastatic cancer. In an oligometastatic state, cancer

invasion is milder and is not susceptible to spread throughout the body. These patients might benefit from aggressive local radiation, as oligometastatic tumors have a low metastatic burden. It has been reported that patients with oligometastatic NSCLC limited to the intrapulmonary or extrapulmonary nodules benefit from surgical resection.[4–7] Recently, many studies have recommended less invasive ablative techniques to treat oligometastasis, such as radiotherapy.[8–11] In this study, we investigated the outcomes and risk factors of NSCLC patients with oligometastasis at diagnosis treated with radiation therapy to the residual lesions.

Methods

Study population

From January 2012 to August 2015, the records of 323 patients with histologically confirmed NSCLC were retrospectively reviewed from the medical record query system at the Cancer Center, Renmin Hospital of Wuhan University.

Eligible patients were aged ≥ 18 years with histologically confirmed NSCLC and < 5 distinct measurable sites of disease (oligometastatic disease). Eligible patients had received four to six cycles initial of platinum-based ChT, and if the tumor responded to the initial treatment and no new metastases were detected by the end of ChT, the residual sites were radiated with a total dose of 56–66 Gy (2 Gy in 28–33 fractions). Three-dimensional conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT) were implemented. Additional eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1.The gross tumor volume (GTV) was delineated according to computed tomography (CT) scans or magnetic resonance imaging (MRI). The planning target volume (PTV) was 0.5–0.8 cm with daily kV imaging.

Patients were evaluated approximately one to three months after the completion of therapy. Treatment was evaluated according to Response Evaluation Criteria in Solid Tumors. Patients underwent follow-up imaging at intervals of three months and received additional ChT and palliative radiotherapy if necessary. Ultimately, 95 patients met the study criteria.

Statistical analysis

Overall survival (OS), progression-free survival (PFS), acute toxicity, and progressive sites were evaluated. Acute toxicity was scored according to Common Terminology Criteria for Adverse Events version 3.0. The Kaplan–Meier method was used to estimate OS and PFS probabilities.

Results

Patients

Patient characteristics are listed in Table 1. All patients had a Karnofsky performance status (KPS) score of ≥ 70 or ECOG PS of 0–1. The median age was 60 (range: 52–69) years, younger than the general NSCLC population. Adenocarcinoma (ADC) was the most prevalent NSCLC subtype, accounting for 51% of cases, followed by squamous cell carcinoma (SCC) at 41%, while the remaining 8% were "other" histologies (large cell/neuroendocrine/not specified). A total of 24% of eligible patients (n = 23) harbored an *EGFR* mutation. Patients progressed with brain (n = 12), bone (n = 16), lung (n = 16), liver (n = 14), and adrenal gland (n = 5) metastases, pleural effusion (n = 5), or metastases at mixed sites (n = 27). Most patients had limited metastasis: over 50% had solitary metastasis. Approximately 28% of patients (n = 27) had metastases at ≥ 2 sites. The median follow-up time from diagnosis to current analysis was 35 (range: 2–109) months.

Table 1 Patient characteristics

Characteristics	No. of patients (%)* (n = 95)
Age at original diagnosis, years	
Median (range)	59 (31–80)
Gender	
Male	67 (71)
Female	28 (29)
Performance status	
ECOG PS 0	73 (77)
ECOG PS 1	22 (23)
Metastasis location	
Brain	12 (13)
Lung	16 (17)
Adrenal	5 (5)
Liver	14 (15)
Bone	16 (17)
Pleural effusion	5 (5)
Mixed	27 (28)
Histology	
Adenocarcinoma	48 (51)
SCC	39 (41)
Otherwise	8 (8)
EGFR mutation	
Positive	23 (24)
Negative	67 (71)
Unknown	5 (5)
Nodal status	
N0/N1	44 (46)
N2/N3	51 (54)

ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous cell carcinoma. *Percentages may not add to 100% because of round-off error.

Chemotherapy and radiation outcomes

Patients received induction ChT according to their pathology: gemcitabine-nedaplatin for SCC (n = 38) and pemetrexed-nedaplatin for ADC (n = 27). SCC/ADC were also treated with other ChT regimens. Twelve patients with *EGFR* mutations received erlotinib or another EGFR-tyrosine kinase inhibitor (TKI) for ≥ 3 months. Most patients received six cycles of ChT (n = 73) to achieve a good PS.

Residual primary lesions were radiated with a median dose of 60 Gy (range: 56–66 Gy) and a median daily dose of 2 Gy (range: 1.8–2 Gy). Before ChT, patients with brain metastasis were radiated with 30 Gy to the whole brain at a median daily dose of 3 Gy. Patients with bone metastasis were radiated to 50 Gy with a daily dose of 5 Gy. Only five patients (5%) were administered paclitaxel-nedaplatin concurrent radiochemotherapy after induction ChT.

Survival rates and relapse outcomes

By the end of the follow-up period, 67 patients had died. The median survival duration of all patients was 15 (95% confidence interval 6–40) months and the median time to relapse was 11 (95% confidence interval 4–24) months. The one-year and two-year OS rates of the whole cohort were 58% and 23%, respectively (Fig 1). The locoregional relapse rate was 19% (18 patients, 8 of which relapsed at the radiated site) and 50 of the original 95 patients developed new distant metastases: brain (n = 14), bone (n = 11), lung (n = 10), liver (n = 7), adrenal gland (n = 5), and other sites (n = 3).

Complications

The entire group completed the treatment process without experiencing unacceptable hematological toxicity. The incidence of severe (grade ≥ 3) acute esophageal toxicity was 18% (17/95). The pulmonary toxicity rate was a little higher than in previous reports; 7% (7/95) patients had severe (grade ≥ 3) radiation-induced pneumonia.

Discussion

The survival rate of patients with oligometastatic NSCLC widely varies, with progression in 50% of patients occurring within approximately 12 months; however, a number of patients achieve long-term survival. Definitive treatment to primary lung cancer and low-burden thoracic tumors remarkably improves long-term survival. A well-known, important feature of tumors is genetic heterogeneity. Systemic ChT only kills sensitive tumor cells, thus residual heterogeneous cells may survive and relapse if intervention is discontinued. Therefore, given tumor heterogeneity, radiotherapy to residual chemoresistant tumor cells may impact patient survival.

Our results indicate that NSCLC patients with oligometastasis benefit from local radiation to residual sites. However, it is not clear whether prolonged survival is unique to specific patients with indolent tumors or the result of therapeutic intervention. Several studies have reported that patients with oligometastasis might benefit from aggressive local radiotherapy, but almost all were retrospective single arm studies. Recently, two randomized phase II trials (NCT00887315 and NCT01446744) were

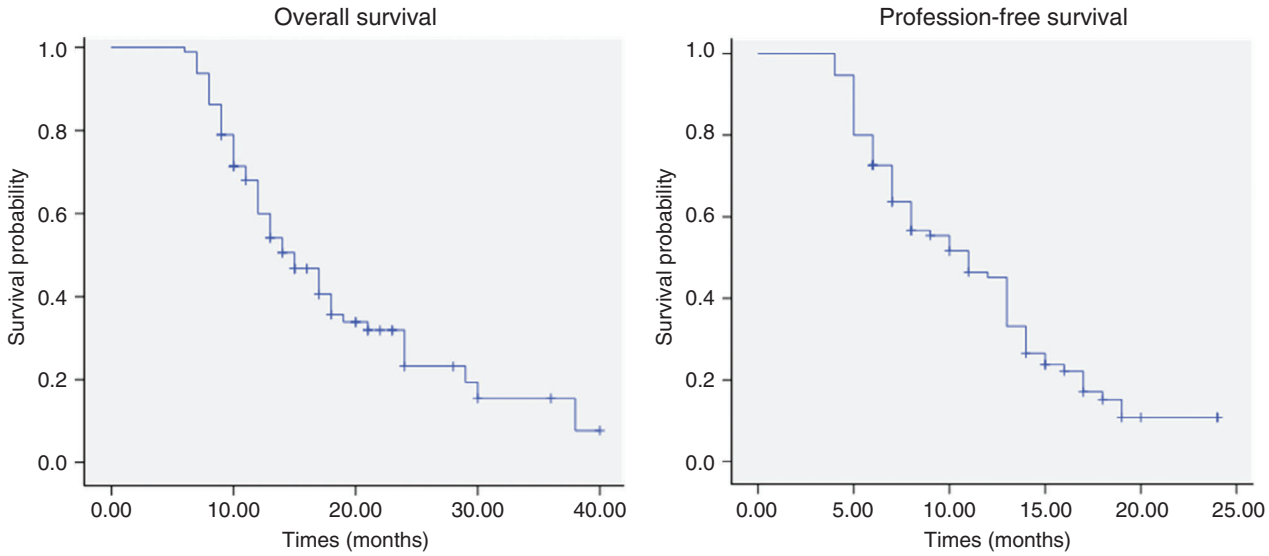

Figure 1 Kaplan–Meier survival estimates from the date of treatment initiation.

initiated for patients with oligometastatic NSCLC. Unfortunately, both trials were discontinued because of slow accrual. The only controlled data in the literature that supports the ablative treatment of oligometastatic NSCLC pertains to brain metastasis. As reported, patients with solitary brain metastasis substantially benefit from primary site radiation compared to patients not administered primary site radiation, with corresponding median OS rates of 15.5 versus 5.9 months, respectively.[12] Nonetheless, other randomized trials have investigated if long-term survival can be improved for specific patients with oligometastasis after systemic ChT. For example, the phase II trial (NCT01446744) is randomizing patients in Canada and the Netherlands with controlled primary tumors of ≤ 5 metastases to stereotactic ablative body radiotherapy to all residual cancer versus groups administered no radiotherapy.[13]

Although some patients achieve long-term survival, most cancer progresses after therapeutic intervention. Thus patient selection is the key to trials of long-term survival of patients with oligometastatic NSCLC. Our results indicate that patients with SCC, good PS, and small lesions (T1,2) achieve longer survival. Patients with *EGFR* mutations receiving TKI therapy also have better survival. Patients with mixed metastatic sites had the shortest median survival, while patients with adrenal metastases had the longest median survival. ChT-effective stable disease is significantly associated with better survival than insensitive stable disease. These factors will influence the clinical strategies and design of future prospective randomized studies. In our study, nodal status and the number of distant metastatic sites were not associated with survival outcome, probably because most patients (72%) developed metastasis at a single site.

Although aggressive radiotherapy for specific patients with oligometastasis shows better survival rates, the risk of treatment-related toxicity exists.[14,15] With respect to toxicity outcomes, the incidence of severe (grade ≥ 3) acute esophageal toxicity in our cohort was similar to that in a published series of patients with metastasis or non-metastasis, but the incidence of pulmonary toxicity was higher than in many previous reports.[16,17] Seven patients (7%) developed severe radiation-induced pneumonitis. According to our clinical inspection, three kinds of patients are susceptible to radiation pneumonitis: (i) patients with poor pulmonary function and previous severe ChT complications; (ii) if the radiation field is limited to the upper or inner lung or mediastinum; and (iii) if the radiation volume is too large. As patients with metastasis are traditionally administered palliative treatments, it is incumbent upon physicians to demonstrate that the escalation of treatment (with attendant risks of side effects or complications) is associated with gains in survival and/or quality of life.

Finally, it must be emphasized that systemic therapy is essential for metastatic NSCLC treatment, including oligometastasis. Initial ChT followed by either switch/continuation maintenance or observation remains the standard of care in this context, and local radiation to primary or metastatic sites should be considered in the scenario of a clinical trial, as is currently being undertaken at our hospital.

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Disclosure

No authors report any conflict of interest.

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