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Originial article

Receipt of thoracic radiation therapy and radiotherapy dose are correlated with outcomes in a retrospective study of three hundred and six patients with extensive stage small-cell lung cancer

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ABSTRACT

Background: The importance of the thoracic radiation therapy (TRT) dose has not been clearly defined in extensive stage small-cell lung cancer (ES-SCLC) and it is unclear whether improved TRT dose translates into a survival benefit.

Methods: 306 patients with ES-SCLC were retrospectively reviewed, of which 170 received IMRT/CRT fractionation RT after ChT, and 136 received chemotherapy (ChT) alone. We adopted the time-adjusted BED (tBED) for effective dose fractionation calculation. Due to the nonrandomized nature of this study, we compared the ChT + RT with ChT groups that matched on possible confounding variables.

Results: Patients achieved 2-year OS, PFS and LC rates of 19.7%, 10.7% and 28.4%, respectively. After propensity score matching, (113 cases for each group), the rates of OS, PFS and LC at 2 years were 21.4%, 7.7% and 34.5% for ChT + TRT, and 10.3% ($p < 0.001$), 4.6% ($p < 0.001$) and 6.3% for ChT only ($p < 0.001$), respectively. Among propensity score matching patients, 56 cases for each group received the high dose (tBED > 50 Gy) TRT and received low dose (tBED $\leq$ 50 Gy) TRT. Two-year OS, PFS and LC rates were 32.3%, 15.3% and 47.1% for the high dose compared with 17.0% ($p < 0.001$), 12.9% ($p = 0.097$) and 34.7% ($p = 0.029$) for low dose radiotherapy.

Conclusions: TRT added to ChT improved ES-SCLC patient OS. High dose TRT improved OS over lower doses. Our results suggest that high-dose thoracic radiation therapy may be a reasonable consideration in select patients with ES-SCLC.

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Lung cancer represents the leading cause of death among all malignancies [1,2]. Approximately, 13% of lung cancers are classified histologically as small cell lung cancer (SCLC), with approximately two-thirds of cases presenting with extensive stage disease (ES-SCLC) [3–5]. Clinically, SCLC typically presents with bulky mediastinum disease with an early propensity for distant metastases, but often strong initial responses to ChT and radiotherapy. Mortality of SCLC remains high, especially in patients with ES-SCLC, which has a 5-year overall survival (OS) of only 2% [6].

Limited stage SCLC (LS-SCLC) patients have improved local control (LC) and OS when adding thoracic radiotherapy (TRT) to ChT, resulting in median survival times of 16–24 months [7,8]. For ES-SCLC patients, ChT is the standard of care and results in a median survival of approximately 7–12 months [7]. In these patients, TRT has traditionally been used only to palliate local symptoms. However, results from a recently published randomized clinical trial indicated that addition of TRT to ES-SCLC who responded to ChT lowered the rates of relapses and improved OS [9]. This result has not been consistently demonstrated, however, as RTOG 0937 demonstrated a delay in progression of disease but no improvement in 1-year OS with addition of consolidative extra-cranial irradiation [10]. Therefore, additional data assessing the potential benefit of TRT for ES-SCLC are needed. Furthermore, the importance of the TRT dose remains undefined for ES-SCLC. This investigation, conducted by a Chinese cancer research center, focuses on the verification of the efficacy of TRT for ES-SCLC to decrease recurrence rates and improve OS and to find the appropriate dose for TRT in ES-SCLC.

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Materials and methods

Patients and evaluation

Between May 2010 and May 2015, 306 consecutive ES-SCLC patients without any prior treatment were systemically studied (see Fig. 1). All SCLC patients were diagnosed upon typical clinical indicators and an assessment of histopathological results [11]. Staging was performed by physical examination, and test of full blood count and serum biochemistry, as well as imaging with chest, abdomen and pelvis computed tomography (CT), brain magnetic resonance imaging (MRI), and bone scan (ECT) for all patients, whereas PET/CT was used in some patients (82, 26.8%). The ES-SCLC diagnostic criteria included AJCC (7th Edition) stage IV (T any, N any and M1a/b) or T3-4 due to patients having multiple lung nodules that were too extensive for local therapy or had tumor or nodal volumes that were too large to be safely included in radiation plan [12].

Treatment strategy

All ES-SCLC patients were administered ChT, with some receiving or not receiving TRT. All patients received EP (30 mg/m^2 cisplatin from days 1 to 3; 100 mg etoposide from days 1 to 5), CE (500 mg carboplatin for day 1; 100 mg etoposide from days 1 to 5) or EP-like regimens (platinum-based ChT) as the first-line treatment. Patients received a median of six ChT cycles.

Overall, TRT was administered to 170 (55.6%) patients following ChT, whereas the remaining 136 (44.4%) patients received ChT only.

The gross target volume (GTV) encompassed the primary tumor and any positive lymph nodes, whereas the clinical target volume (CTV) was expanded from the GTV by a 0.5–0.8 cm uniform margin and included the draining area of any positive lymph nodes. In addition, the planning target volume (PTV) included the CTV plus a margin of 0.5–1.0 cm. Some patients with too extensive gross disease for a safe radiation plan or significant extrathoracic disease extent with more than 1 organ residual metastasis after ChT were treated with TRT to a planning gross target volume (PGTV). PGTV was defined as GTV plus a 0.5–1.0 cm margin. Radiotherapy was administered using 6 MV photons by a linear accelerator. A few patients received prophylactic cranial irradiation (PCI) (13.5% in ChT + TRT and 3.0% in ChT alone).

The median radiation dose was 60 Gy. Because of different radiation fractionations employed clinically, we use biological effective dose (BED) in RT for conversion between different fractionation schemes to estimate the malignant and normal biological effects in tissues [13–15]. Considering the time efficiencies, we adopted the time-adjusted BED (tBED) formula [16,17], which is derived from the LQ model and is defined as [18]:

$$\mathrm{tBED} = \mathrm{nd}[1 + d/(\alpha/\beta)] - (0.693t)/(\alpha \mathrm{Tpot})$$

where n represents the fractions in the treatment, d is the prescription dose of one fraction, t is the time of radiotherapy, α/β is the ratio of radio-sensitivity coefficients, and Tpot is the potential doubling time, which is a cell kinetic parameter that indicates the rate at which cells are proliferating in untreated tumor. According to the previous reports about SCLC cell potential doubling time, Tpot range is 2.6–8.6 days [19–21], we consider the mean 5.6 days as the Tpot value [18].

38 received hypofractionation TRT (30–48 Gy/3 Gy/10-16f, tBED = 33.6–53.7 Gy) and the other 132 patients received conventional fractionation TRT (50–60 Gy/1.8–2.1 Gy/25-30f, $n = 148$, tBED = 46.0–55.1 Gy).

Oligometastasis

Based on the authors' report [22], we defined the concept of ES-SCLC oligometastasis as follows: (1) only one organ metastasis or metastatic lymph node metastasis (able to be covered by a safe radiotherapy portal); (2) multiple brain metastases (treated with whole brain radiotherapy); or (3) continuous vertebral bone metastases treated in a single radiotherapy field.

Statistical analysis

The solid tumor response based on RECIST 1.0 [23] was utilized as criteria to assess the initial treatment responses. The baseline evaluation was performed every other cycle during the ChT, and the entire group of patients also received evaluation every 6–8 weeks post-treatment until disease progression. Acute toxicities were scored according to the CTCAE (version 4.0), whereas late toxicities were graded according to the RTOG radiation morbidity scoring criteria [24].

OS, progression-free survival (PFS), and LC were defined from the first date of the treatment to the time of events or last follow-up and were computed from the Kaplan–Meier method. The comparison of survival curves between different groups was conducted using the log-rank test, and the categorical data were compared based on the chi-square method. Kaplan–Meier's method was used to perform univariate survival analysis to find the correlation between OS and clinical features, including gender, the smoking index, Karnofsky's performance status (KPS) score, age, weight loss, metastatic organs (number), presence or absence of brain metastasis, cycles of ChT, and receipt or no receipt of TRT. The above features were used as parameters to feed a multivariate model, and the significant variables were determined by a Cox proportional hazards algorithm using the backward–forward and stepwise method. SPSS software v18.0 (SPSS Inc, Chicago, IL) and R 2.8.0 was used to perform the statistical analyses. Because of the nonrandomized nature of this study, we compared the ChT + RT and ChT groups on propensity score matched (PSM) analysis controlling for possible confounding variables. A group of 188 patients with ChT + RT was matched to 136 patients with ChT based on the baseline age, gender, smoking index, weight loss >5%, KPS score, stage, location of metastatic organs, metastatic organs number, ChT cycles number, and response to ChT.

Results

The male vs. female ratio was 3.5:1. The age of group was between 18 and 85 years with a median age of 60 years, and 29.4% of patients had ages above 65 years. Most patients (80.4%) had a heavy smoking history, 92.8% presented with good performance status (KPS $\geq$ 80), and 66.3% had more than 1 organ involved with metastasis.

Following initial ChT, complete response (CR) and partial response (PR) rates were 0 ($n = 0$), 67.6% ($n = 207$), whereas the stable disease (SD) and progression disease (PD) rates were14.7% ($n = 45$) and 17.6% ($n = 54$). In ChT + RT group, 89.4% ($n = 152$) patients achieved PR, 0.6% ($n = 1$) had SD and 10.0% ($n = 17$) had PD after ChT. The addition of TRT significantly improved the initial response. Fifteen patients, having mediastinal PD while receiving ChT receiving palliative radiation therapy, achieved CR or PR.

Based on the 34.4 months median follow up, the OS, PFS and LC at 2 years were 18.8%, 9.7% and 25.8%, respectively. In total, 248 patients died from SCLC, and 58 were still alive with SCLC.

The significance of prognosis with OS was assessed based on the characteristics of patients and disease characteristics. Our univariate analysis demonstrated that male, stage IV disease, involved organs except brain, $\geq$2 metastatic organs, have no response to

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