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Outcomes of gefitinib therapy for disease recurrence in medically inoperable stage I lung adenocarcinoma patients with active EGFR mutations receiving stereotactic body radiotherapy: a single-institute retrospective study

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Introduction: Anticancer therapy for disease recurrence in medically inoperable stage I lung adenocarcinoma patients receiving stereotactic body radiotherapy (SBRT) has not been previously reported. Gefitinib is tolerable and effective in patients with active epidermal growth factor receptor (EGFR) mutations who have an advanced age and/or a low performance status, but whether gefitinib improves the survival of such patients with disease recurrence after SBRT remains unclear.

Patients and methods: We retrospectively evaluated overall survival after disease recurrence in patients with active EGFR mutations who received gefitinib (GEF group) and patients without active EGFR mutations who did not receive gefitinib (non-GEF group).

Results: During a follow-up period with a median time of 36.0 months, disease recurrence occurred in 10 of 20 patients with medically inoperable stage I lung adenocarcinoma who received SBRT (2 cases with local tumor recurrence alone and 8 cases with lymph node and/or distant metastasis). The median age or the median Charlson comorbidity index score were 84 years and 2 in the GEF group (n = 4) and 81 years and 2 in the non-GEF group (n = 6), respectively. Two cases in the GEF group received chemotherapy after first-line gefitinib therapy. Two cases in the non-GEF group received chemotherapy, but the others received best supportive care alone. The median overall survival time from disease recurrence was significantly different between the 2 groups (27.3 vs. 3.6 mo, $P = 0.038$). Two cases with grade 2 radiation pneumonitis did not have a recurrence of pneumonitis during gefitinib therapy.

Conclusions: Gefitinib might be useful as a salvage therapy in patients who desire to continue anticancer treatment.

Keywords: Adenocarcinoma, Stereotactic body radiotherapy, Gefitinib, EGFR mutations

Surgical resection is a standard treatment for stage I non–small cell lung cancer (NSCLC), but it is often not feasible for early lung cancer patients with an advanced age, severe comorbidities or other medical conditions. Radiotherapy (RT) can be useful as a therapeutic alternative for medically inoperable stage I NSCLC patients[1–4]. However, as the prognosis of patients receiving conventional RT has been inferior to that of patients receiving surgical resection because the radiation dose of conventional RT was too low to control the local tumor, hypofractionated high-dose stereotactic body RT (SBRT) has recently been performed in patients with relatively small NSCLC lesions.

SBRT is an irradiation technique using multiple nonopposing beams or large angle arc rotations to enable to the precisely targeted irradiation of lung cancer while minimizing the radiation dose to normal tissue. As the dose-per-fraction increases allow biological doses that are up to twice as high as conventional RT, SBRT can enable local tumor control rates of ~90% or the 3-year overall survival (OS) rates of 56%–83% without any significant decline of quality of life after the treatment[5–9]. SBRT plays an important role in the management of medically inoperable stage I NSCLC patients[10]. The 3-year disease-free survival (DFS) rates of patients receiving SBRT has been reported to range from 48% to 70%[5,7,8] and half of all patients exhibit recurrent lung cancer after SBRT. Nonetheless, sequential therapy for disease recurrence has not been previously reported, possibly because patients receiving SBRT do not expect to receive sequential therapy because of either an advanced age or an impaired medical condition resulting in death as a result of severe comorbidities.

We have noticed the presence of epidermal growth factor receptor (EGFR) mutations in such patients. EGFR tyrosine kinase

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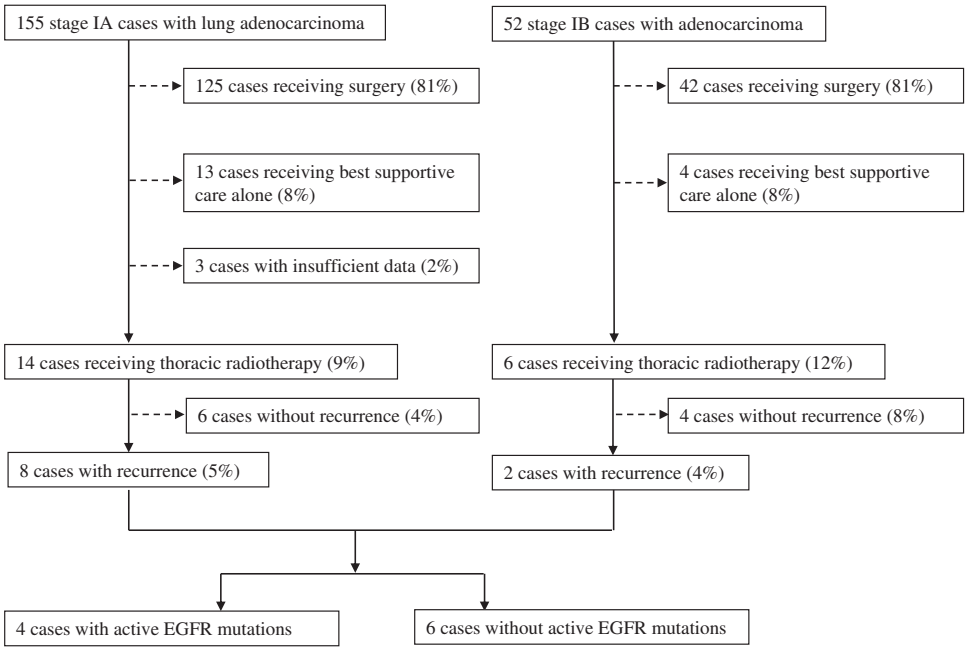

Figure 1. Study flowchart. EGFR indicates epidermal growth factor receptor.

inhibitors (EGFR-TKI) are associated with a high objective response rate and long progression-free survival or OS periods in patients with advanced NSCLC with active EGFR mutations[11–17]. In addition, gefitinib is tolerable and effective in NSCLC patients aged 75 years and above or with an Eastern Cooperative Oncology Group performance status (PS) score of 2–4[18,19]. Here, we retrospectively evaluated the efficacy and tolerability of gefitinib in patients with medically inoperable stage I lung adenocarcinoma and disease recurrence after SBRT.

Patients and methods

This work is registered at Research Registry with UIN 4482 and has been reported in line with the STROCSS criteria[20]. This single-institute retrospective study was approved by the Institutional Review Board of the Kumamoto Regional Medical Center (approval date, March 27, 2018; approval number, 17-038). Data for 207 patients with clinical stage I lung adenocarcinoma were retrospectively retrieved from the database of electronic medical records: all patients had been treated during a 7-year period from April 1, 2010 to March 31, 2017. These patients had been diagnosed as having adenocarcinoma using bronchoscopy and/or percutaneous needle biopsy at our institute and had undergone the torso computed tomography (CT), brain magnetic resonance imaging, and F-18 fluorodeoxyglucose positron emission tomography examinations. Their diseases had been staged according to the guidelines of the Union for International Cancer Control TNM classification of malignant tumors (seventh edition). Their EGFR mutation statuses had been examined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method[21].

One-hundred twenty-five (81%) of the 155 stage IA cases and 42 (81%) of the 52 stage IB cases underwent surgery. Eight percent of the stage IA cases and 8% of the stage IB cases received best supportive care (BSC) alone. The reasons for not receiving surgery were an advanced age (n = 8; median patient age, 87 y), a previous history of a lower lobe lobectomy for lung cancer (n = 5), poor pulmonary function because of chronic lung disease (n = 2), and severe cardiovascular disease (n = 2). Three cases with insufficient data were excluded from this study. SBRT was performed in 14 cases (9%) with stage IA disease and in 6 cases (12%) with stage IB disease (**Fig. 1**).

SBRT was planned and performed at the Kumamoto Radiosurgery Clinic (Kumamoto, Japan). Patients were immobilized in supine position with arms above the shoulder using a Vac-Lok and HipFix airbag system (CIVCO Medical Solution, Kalona, IA). They were planned and treated on a Novalis Tx system with an ExacTrac and On-Board Imager stereotactic body positioning system (BrainLab, Tokyo, Japan). The clinical tumor volume was delineated as visualized on the pulmonary CT windows (GE Lightspeed RT16; GE Healthcare, Tokyo, Japan) and the internal target volume was created individually according to the internal respiratory motion. The planned target volume margin was 5–10 mm in all directions. An intensity modulated arc therapy (Valian Medical Systems, Tokyo, Japan) was performed. The median biological effective dose (BED_{10}) was defined as $nd[1 + d/\alpha/\beta]$, with n being the number of fractions, d being the daily single fraction dose; the α/β value for the tumor tissue was set at 10 Gy. According to the Response Evaluation Criteria in Solid Tumours version 1.1, complete response (CR) was defined as disappearance of all target lesions, partial response (PR) was defined as $\geq 30\%$ decrease in the sum of the longest diameters of target lesions compared with the baseline, progressive disease (PD) was defined as $\geq 20\%$ increase in the sum of the longest diameters of target lesions compared with the smallest-sum diameter recorded and/or the appearance of one or more new lesions and stable disease (SD) was defined as neither PR or PD. Adverse events were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.0.

Thin-section CT images were obtained using a Brilliance 64 CT system (Philips, Tokyo, Japan) and were evaluated independently by both a radiologist and a respirologist. Nonsolid nodules were defined as nodules within which none of the lung parenchyma was obscured; part-solid nodules were defined as nodules containing patches of completely obscured lung parenchyma; and solid nodules were defined as nodules within which the lung parenchyma was completely obscured[22].

Comorbidities were documented at the initiation of SBRT and were defined according to the Charlson comorbidity index (CCI), which is widely used to evaluate the severity of comorbidities and consists of 17 comorbid conditions (a score of comorbidity) including diabetes mellitus (1), cerebrovascular disease (1), cardiovascular disease (1), chronic lung disease (1), connective tissue disease (1), neoplasm (2), and others[23].

The statistical analysis was performed on a computer using the Stat View J 5.0 statistical program (SAS Institute Inc., Berkeley, CA). Differences in clinical data between 2 independent samples were tested using the Mann-Whitney *U* test. Categorical data were analyzed using the χ^2 test or the Fisher exact probability test. Univariable analyses of clinical variables were performed to identify possible risk factors affecting OS. The DFS and the OS were estimated using the Kaplan-Meier method. A 2-tailed *P*-value of <0.05 was considered to indicate a statistically significant difference.

Results

Survival in patients receiving SBRT

The patient and disease characteristics are summarized in **Table 1**. The median patient age was 83 years at the initiation of SBRT. In the studied group, 20% were women, 10% had a PS score of 2, 65% were past or current smokers, 90% had comorbidities with a median CCI score of 2, 90% had solid nodules and 70% had a stage IA disease. There were 7 cases with active EGFR mutations and 13 cases without active EGFR mutations (10 cases with a wild-type EGFR mutation and 3 cases with an unknown status). All the patients completed SBRT with a median daily dose of 6 Gy, a median fraction number of 13 fractions, a median total dose of 60 Gy and a median BED_{10} dose of 96 Gy. Of the 20 tumors after SBRT, 4 tumors achieved CR, 12 achieved PR and 4 achieved SD. Five cases exhibited grade 2 radiation pneumonitis and 3 received the oral administration of prednisolone (0.5 mg/kg). There were no adverse events except grade 1 dermatitis (n = 2) and grade 2 esophagitis (n = 2).

During a median 36.0-month follow-up period from the initiation of SBRT, 10 of the 20 cases receiving SBRT experienced disease recurrence (2 cases with local tumor recurrence alone and 8 cases with lymph node and/or distant metastasis); the local control rate was 80%. Disease recurrence was observed in 4 of the 7 cases with active EGFR mutations and in 6 of the 13 cases without active EGFR mutations. The median DFS time and the 3-year DFS rate were 45.3 months and 64% for the cases with active EGFR mutations and 37.5 months and 56% for the cases without active EGFR mutations (**Fig. 2A**). Eight cases died of cancer and 2 cases died from another disease. The median OS time and the 3-year OS rate were higher for the cases with active EGFR mutations than for those without active EGFR mutations (median OS times, 72.8 vs. 55.0 mo; 3-year OS rates, 100% vs. 59%), but the differences were not statistically significant ($P = 0.301$) (**Fig. 2B**).

Table 1

Patient and disease characteristics in patients receiving SBRT.

		No. Patients (%)
Age (y)		83 (69–94)
Sex	Women	4 (20)
Performance status	0, 1	18 (90)
	2	2 (10)
Smoking history	Past or current smokers	13 (65)
Charlson comorbidity index		2 (0–4)
Comorbidities	Yes	18 (90)
	Chronic lung disease	8 (40)
	Diabetes mellitus	4 (20)
	Cerebrovascular disease	3 (15)
	Cardiovascular disease	2 (10)
	Connective tissue disease	1 (5)
	Neoplasm	6 (30)
Thin-section CT images	Nonsolid nodules	0
	Part-solid nodules	2 (10)
	Solid nodules	18 (90)
Clinical stage	IA	14 (70)
	IB	6 (30)
EGFR mutation	Deletion of exon 19	2 (10)
	L858R in exon 21	5 (25)
	Wild type or unknown	13 (75)
SBRT	Daily dose	6 (2–12)
	Fraction number	10 (4–35)
	Total dose	60 (48–73)
	BED_{10}	96 (84–106)
Radiation pneumonitis (grade 2)		5 (25)
Recurrence of cancer	Yes	10 (50)
Recurrence sites	Local tumor alone	2 (10)
	Lymph node and/or distant metastasis	8 (40)

Data are number (%) or median (range).

BED_{10} indicates biological equivalent dose using an alpha-beta for tumor tissue of 10 Gy; CT, computed tomography; EGFR, epidermal growth factor receptor; SBRT, stereotactic body radiotherapy.

Survival in patients receiving gefitinib

We divided the 10 patients with disease recurrence into 2 groups: patients with active EGFR mutations who received gefitinib (GEF group; n = 4) and patients without active EGFR mutations who did not receive gefitinib (non-GEF group; n = 6). The median patient age was 84 years in the GEF group and 81 years in the non-GEF group. In the GEF group, the percentages of women (50% vs. 17%) and cases with stage IA disease (100% vs. 67%) were higher and the percentages of cases with smoking history (50% vs. 83%) and a median BED_{10} dose (89 Gy vs. 94 Gy) were lower than those in the non-GEF group (**Table 2**). Patients in the GEF group experienced anemia (n = 1), the elevated levels of alanine aminotransferase and asparate aminotransferase (n = 1), skin rash (n = 4), diarrhea (n = 2), and anorexia (n = 1), but there were no adverse events with grade ≥ 3 (**Table 3**).

Two cases in the GEF group received monotherapy with third-generation cytotoxic agents after the failure of first-line gefitinib therapy. Two cases in the non-GEF group received first-line chemotherapy including carboplatin-based doublet regimens, whereas the others received BSC alone. One case in the non-GEF group exhibited grade 3 drug-induced pneumonitis during chemotherapy and was treated with an oral administration of

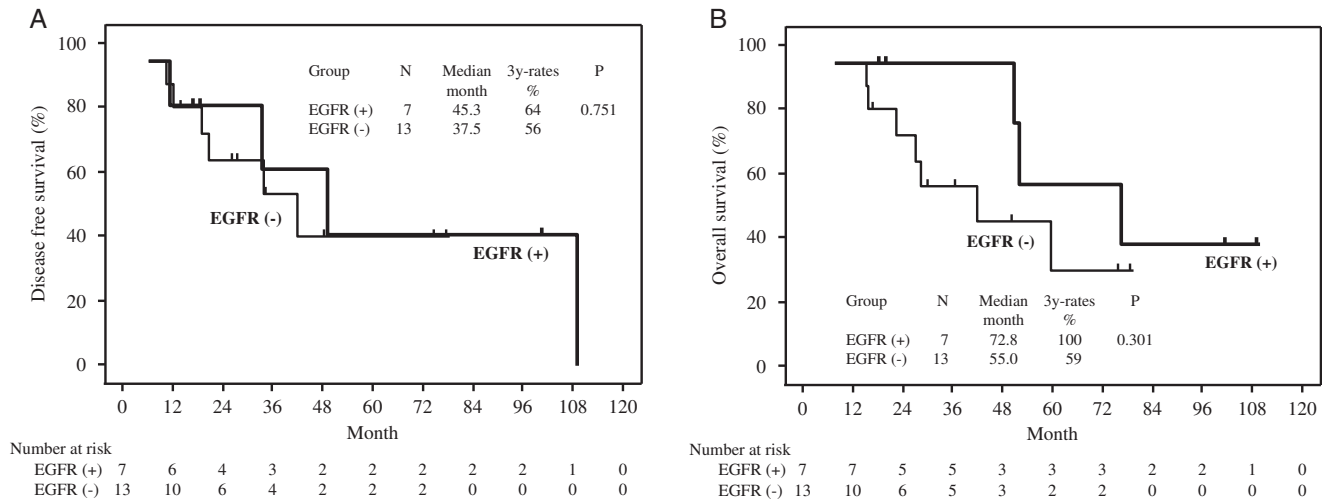

Figure 2. Disease-free survival (A) and overall survival (B) after the initiation of stereotactic body radiotherapy in patients with active EGFR mutations and patients without active EGFR mutations. EGFR indicates epidermal growth factor receptor.

Table 2

Patient characteristics at the time of disease recurrence in patients who received gefitinib (GEF group) and in patients who did not receive gefitinib (non-GEF group).

		GEF (N = 4)	Non-GEF (N = 6)
EGFR mutation	Yes	4 (100)	0
	Deletion of exon 19	2 (50)	0
	L858R in exon 21	2 (50)	0
Age (y)		84 (77–89)	81 (69–87)
Sex	Women	2 (50)	1 (17)
	Men	2 (50)	5 (83)
Performance status	0, 1	4 (100)	5 (83)
	2	0	1 (17)
Smoking history	Past or current smokers	2 (50)	5 (83)
Charlson comorbidity index		2 (1–4)	2 (0–4)
Thin-section CT images	Part-solid nodules	0	1 (17)
	Solid nodules	4 (100)	5 (83)
Clinical stage	IA	4 (100)	4 (67)
	IB	0	2 (33)
SBRT	BED_{10}	89 (84–96)	94 (91–96)
Radiation pneumonitis (grade ≥ 3)		2 (50)	0
Anticancer therapy for disease recurrence after SBRT			
First-line	Gefitinib	4 (100)	0
	Carboplatin-based therapy	0	1 (17)
	Monotherapy	0	1 (17)
	Best supportive care alone	0	4 (67)
Second-line or thereafter	Monotherapy	2 (50)	0
	Best supportive care	2 (50)	0
Adverse events (grade ≥ 3)	Drug-induced pneumonitis	0	1 (17)
	Neutropenia	1 (25)	1 (17)

Data are number (%) or median (range).

BED_{10} indicates biological equivalent dose using an alpha-beta for tumor tissue of 10 Gy; CT, computed tomography; EGFR, epidermal growth factor receptor; GEF, gefitinib; SBRT, stereotactic body radiotherapy.

prednisolone (0.5 mg/kg). Two of the 5 cases with grade 2 radiation pneumonitis had active EGFR mutations, but pneumonitis did not recur during gefitinib therapy. Grade 3 neutropenia was found during chemotherapy in one case in each of the group. The median OS times after disease recurrence were 27.3 months in the GEF group and 3.6 months in the non-GEF group and this difference was significant ($P = 0.038$) (**Fig. 3**).

Discussion

The 3-year OS rates for medically inoperable stage I NSCLC patients receiving SBRT reportedly range from 56% to 83%[5–9]. In the present study, the 3-year OS rate in patients without active EGFR mutations was 59%, which was slightly lower than the results of previous reports. Onishi et al[6] reported that the local control and survival rates were better in patients receiving SBRT with a BED_{10} of ≥ 100 Gy than in those with a BED_{10} of < 100 Gy. The median BED_{10} dose in our study was 96 Gy (range,

Table 3

Hematological and nonhematological toxicity in patients who received gefitinib (n = 4).

	NT-CTC Grade			
	All	1	2	≥ 3
Hematological toxicity				
Neutropenia	0	0	0	0
Thrombocytopenia	0	0	0	0
Anemia	1	1	0	0
Nonhematological toxicity				
Pneumonitis	0	0	0	0
AST/ALT	1	1	0	0
Rash	4	3	1	0
Diarrhea	2	2	0	0
Anorexia	1	1	0	0

AST/ALT indicates alanine aminotransferase/aspartate aminotransferase; NT-CTC, National Cancer Institute Common Terminology Criteria.

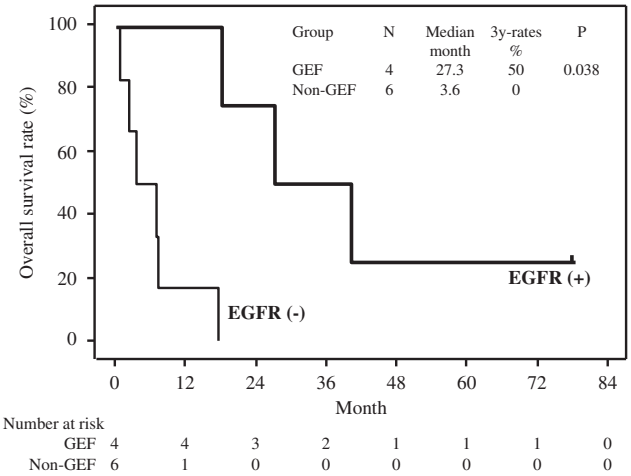

Figure 3. Overall survival after disease recurrence in patients who received gefitinib (GEF group) and patients who did not receive gefitinib (non-GEF group). EGFR indicates epidermal growth factor receptor; GEF, gefitinib.

84–106 Gy) and this may explain the relatively 3-year OS rate. On the other hand, the 3-year OS rate was 100% in the 7 patients with active EGFR mutations who received gefitinib. Our study suggests that gefitinib can improve the prognosis from the time of disease recurrence after SBRT in medically inoperable stage I adenocarcinoma patients with active EGFR mutations.

The Japan Lung Cancer Society guideline[24] recommends that EGFR-negative patients aged 75 years and above or with a PS score of 0–2 receive monotherapy with a third-generation cytotoxic agent or carboplatin-based doublet chemotherapy and that patients with a PS score of 3–4 receive BSC alone. In our study, chemotherapy was performed in only 34% of the patients in the non-GEF group because of an advanced age or the presence of severe comorbidities, although all the patients had a PS score of 0–2 at the time of disease recurrence after SBRT. On the other hand, all the cases in the GEF group received gefitinib, and 50% received sequential monotherapy.

Gefitinib is tolerable and effective in patients with an advanced age or with an impaired physical condition[18,19] and is less toxic than cytotoxic chemotherapy, with the most frequent adverse events being skin rash or diarrhea. In Japan, however, drug-induced pneumonitis caused by gefitinib has been reported as a serious and occasionally fatal adverse event associated with the use of EGFR-TKIs, with an overall prevalence of 3.5% and a mortality rate of 1.6%[25]. In the present study, 2 of the 5 cases with grade 2 radiation pneumonitis had active EGFR mutations, but the pneumonitis did not recur during gefitinib therapy. In addition, the most common adverse events of gefitinib therapy was rash and diarrhea. The incidence of adverse events including pneumonitis reportedly does not increase in patients undergoing thoracic RT with concurrent administration of gefitinib as a radio-sensitizer[26,27]. We suggest that gefitinib is tolerable and effective in patients receiving SBRT and does not increase the risk of other toxicities.

The sample size in our study was relatively small because this was a retrospective study performed at a single institute. Our study, however, is the first to show that gefitinib improves the survival after disease recurrence following SBRT in patients with active EGFR mutations, even if they have an advanced age, severe comorbidities or other medical conditions.

In conclusion, gefitinib might be useful as a salvage therapy in patients who desire to continue anticancer treatment.

Compliance with ethical standards

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval

Institutional Review Boards at the corresponding institutions approved this study.

Sources of funding

No funding for this work was received.

Authors contribution

K.K.: data collection, analysis, writing; H.S., S.F., and S.T.: data collection, analysis.

Conflicts of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Guarantor

Not applicable.

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References

[1] Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. Thorax 2001;56:628–38.
[2] Sibley GS. Radiotherapy for patients with medically inoperable stage I non-small cell lung carcinoma: smaller volumes and higher doses—a review. Cancer 1998;82:433–8.
[3] Qiao X, Tullgren O, Lax I, *et al*. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer 2003;41:1–11.
[4] Tyldesley S, Boyd C, Schulze K, *et al*. Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach. Int J Radiat Oncol Biol Phys 2001;49:973–85.
[5] Nagata Y, Takayama K, Matsuo Y, *et al*. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427–31.

[6] Onishi H, Shirato H, Nagata Y, *et al*. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94–100.
[7] Timmerman R, Paulus R, Galvin J, *et al*. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.
[8] Baumann P, Nyman J, Hoyer M, *et al*. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290–6.
[9] van den Berg LL, Klinkenberg TJ, Groen HJ, *et al*. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. J Thorac Oncol 2015;10:826–31.
[10] Schneider BJ, Daly ME, Kennedy EB, *et al*. Stereotactic body radiotherapy for early-stage non-small-cell lung cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. J Clin Oncol 2018;36:710–9.
[11] Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
[12] Mitsudomi T, Morita S, Yatabe Y, *et al*. West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121–8.
[13] Maemondo M, Inoue A, Kobayashi K, *et al*. North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380–8.
[14] Zhou C, Wu YL, Chen G, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735–42.
[15] Rosell R, Carcereny E, Gervais R, *et al*. Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.
[16] Sequist LV, Yang JC, Yamamoto N, *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327–4.
[17] Wu YL, Zhou C, Hu CP, *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213–2.
[18] Maemondo M, Minegishi Y, Inoue A, *et al*. First-line gefitinib in patients aged 75 or older with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations: NEJ 003 study. J Thorac Oncol 2012;7:1417–22.
[19] Inoue A, Kobayashi K, Usui K, *et al*. North East Japan Gefitinib Study Group. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394–400.
[20] Agha RA, Borrelli MR, Vella-Baldacchino M, *et al*. STROCSS Group. The STROCSS statement: strengthening the reporting of cohort studies in surgery. Int J Surg 2017;46:198–202.
[21] Nagai Y, Miyazawa H, Huqun, *et al*. Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. Cancer Res 2005;65:7276–82.
[22] Henschke CI, Yankelevitz DF, Mirtcheva R, *et al*. ELCAP Group. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053–7.
[23] Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[24] The Japan Lung Cancer Society. Japan Guidelines of Lung Cancer Therapy, 2016 ed. Japan: Kanehara Shuppan; 2017.
[25] Ando M, Okamoto I, Yamamoto N, *et al*. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 2006;24:2549–56.
[26] Niho S, Ohe Y, Ishikura S, *et al*. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol 2012;23:2253–8.
[27] Wang Z, Zhu XX, Wu XH, *et al*. Gefitinib combined with stereotactic radiosurgery in previously treated patients with advanced non-small cell lung cancer. Am J Clin Oncol 2014;37:148–53.