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Salvage surgery for advanced non–small cell lung cancer after response to gefitinib

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI) gefitinib has dramatic efficacy in more than 70% of advanced non–small cell lung cancers with EGFR gene mutations.[1] Some patients with inoperable systemic non–small cell lung cancers demonstrate a down-staging of their cancer to operable disease status after gefitinib treatment. Despite high response rates for EGFR mutant tumors, the median time to progression is about 1 year.[1] The EGFR T790M mutation and *MET* amplification are thought to be the underlying mechanisms of the acquired resistance to EGFR-TKIs. When complete resection of residual disease is possible, the patients can then be considered disease free. We have aggressively performed salvage lung resections for patients with gefitinib responses and demonstrated down-staging to N0M0. The purpose of this study was to assess

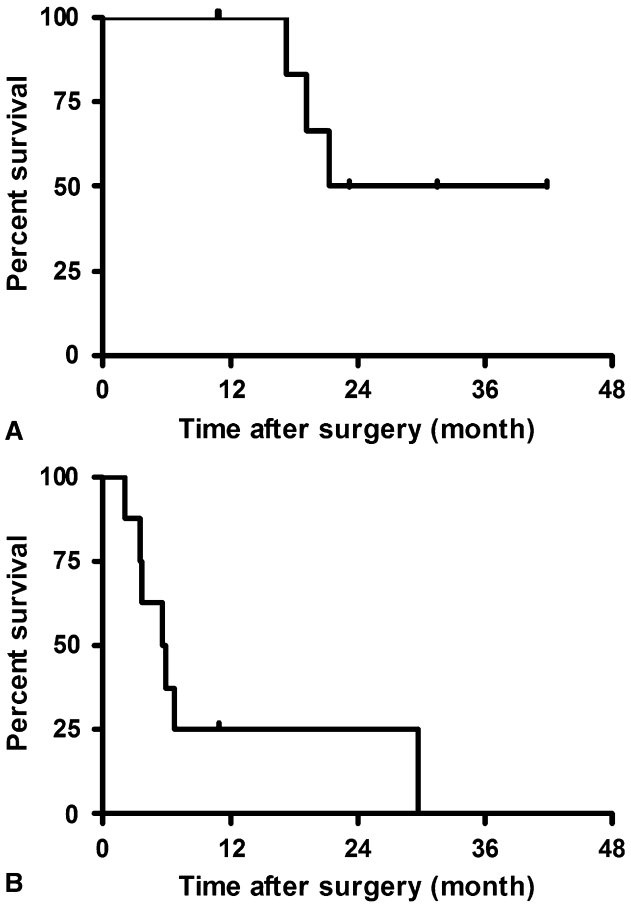

FIGURE 1. A, Overall survival curve of patients who underwent surgical resection after response to gefitinib administration. Median overall survival after surgery was 32 months. B, Recurrence-free survival curve of patients who underwent surgical resection after response to gefitinib administration. Median recurrence-free survival after surgery was 6 months.

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TABLE 1. Patient characteristics

Case	Age (y), sex	Initial CS	Treatment before gefitinib (response)	Gefitinib duration	CS before surgery
1	73, F	cT4(PM)N2M0, IIIB	None	3 mo	cT2N0M0, IB
2	51, F	cT2N3M1(brain), IV	None	3 y	cT1N0M0, IA (local regrowth)
3	58, F	cT2N2M0, IIIA	CDDP + VNR (SD), CBDCA + PTX (SD)	5 mo	cT1N0M0, IA
4	58, F	cT4(D+)N0M0, IIIB	CDDP + GEM (SD)	2 y, 10 mo	cT1N0M0, IA (local regrowth)
5	63, F	cT2N3M1(abd LN), IV	CDDP + TS-1 (PR)	1 y, 4 mo	cT1N0M0, IA (local regrowth)
6	33, M	cT4 (PM, E+)N0M0, IIIB	CBDCA + PTX (SD)	2 mo	cT1N0M0, IA
7	54, M	cT4N3M1(PM), IV	CDDP+DTX (SD)	1 y, 10 mo	cT1N0M0, IA
8	71, F	cT2N3M0, IIIB	None	1 y, 6 mo	cT2N0M0, IB
9	57, F	cT4N0M1(PM), IV	CBDCA + DTX (SD)	Unknown	cT1N0M0, IA

CS, Clinical stage; *EGFR,* epidermal growth factor receptor; *PM,* pulmonary metastasis; *DWD,* died with disease; *AWD,* alive with disease; *CDDP,* cisplatin; *VNR,* vinorelbine tartrate; *SD,* stable disease; *CBDCA,* carboplatin; *PTX,* paclitaxel; *CR,* complete response; *D,* pleural dissemination; *GEM,* gemcitabine; *AWOD,* alive without disease; *abd LN,* abdominal lymph node; *TS-1,* tegafur/gimeracil/oteracil potassium; *PR,* partial response; *E,* malignant pleural effusion; *DTX,* docetaxel. *. Endothelial growth factor receptor mutational analysis was performed on pretreatment biopsy specimens obtained by bronchoscopy.

the perioperative safety and survival benefit of these salvage lung resections.

CLINICAL SUMMARY

After institutional review board approval at each institution, the clinicopathologic profiles of a total of 9 patients were collected by a questionnaire survey in 2009 from 7 institutions belonging to the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group. The questionnaire included the following items: sex, age, smoking history, clinical (pretreatment) stage, response to therapy before gefitinib monotherapy, response to and adverse effects of gefitinib monotherapy, duration of gefitinib administration, withdrawal period of gefitinib before surgery, preoperative clinical stage, surgical procedure, morbidity and mortality of surgery, primary site by lobe, histology, pathologic stage, EGFR mutation status, postoperative therapy, survival time, recurrence, and cause of death.

The patient characteristics are shown in Table 1. All cases were adenocarcinoma, and all had been initially diagnosed as inoperable. Surgery was performed to eradicate residual tumors or local recurrence and regrowth, with a median administration period of 17 months (range, 2–36 months). Gefitinib was terminated before surgery in all cases, with a median withdrawal period of 7 days (range, 1–21 days). Resection was accomplished in all cases, with a median hospital stay of 9 days (range, 6–34 days). There was 1 case of mild liver dysfunction, and there were no deaths. An EGFR mutational analysis of resected specimens or of the pretreatment biopsy specimen (patient 3) was performed in 7 cases. Six of 7 patients harbored EGFR mutations, exon 19 deletions or exon 21 L858R. Two patients also had EGFR-TKI–resistant exon 20 T790M mutations. Four patients who underwent surgery in late study period received gefitinib postoperatively for various durations. Despite the remarkable downstaging of the patients' disease after gefitinib treatment, 7 of 9 patients showed a more advanced pathologic stage than their preoperative clinical stage. Six patients with initial N2-3 disease all had radiologic downstaging to N0 status before attempted resection. Pathologically, 2 patients had persistent N2 disease and 1 had N1 disease. The recurrence-free and overall survivals are shown in Figure 1 (*A* and *B*). The most common site of recurrence was the brain. One patient has been alive without disease for 11 months with the use of adjuvant gefitinib.

DISCUSSION

Our patient population had no serious immediate postoperative morbidity or mortality. Among a total of 41 patients in the literature who underwent lung resection after EGFR-TKI treatment, none died perioperatively.[2-5] Although there has been some concern that preoperative EGFR-TKIs may be associated with impaired wound healing, major lung resection after EGFR-TKI therapy may be feasible.

On the other hand, postoperative survival in the this series was not satisfactory, with a median recurrence-free survival of 6 months. Despite dramatic radiographic downstaging after gefitinib treatment, 7 of 9 patients had further advanced pathologic stages than their preoperative clinical stages. Dramatic radiologic response does not necessarily correlate with cell death. Our results suggest that initially expressed systemic disease was essentially unchanged even after dramatic radiologic response to gefitinib. Surgery after gefitinib treatment should be limited to patients without initial evidence of disseminated and distant metastases. EGFR-TKIs have both higher and more rapid responses, and better toxicity profiles than standard chemotherapy for non–small cell lung cancers harboring EGFR mutation. Preoperative EGFR-TKI treatment strategy should be reevaluated in the neoadjuvant setting for early to locally advanced but operable disease. The optimal duration of EGFR-TKI treatment,

TABLE 1. Continued

Mode of resection	Pathologic stage	EGFR gene status	Adjuvant therapy	Outcome
Lobectomy	pT2N1M0, IIB	Wild type	None	Bone metastasis (6 mo), DWD (1 y, 5 mo)
Lobectomy	pT1N0M0, IA	Exon 19 (del)	None	Brain metastasis (2 mo), AWD (3 y, 6 mo)
Left pneumonectomy	Pathologic CR	Exon 19 (del)*	Gefitinib (2 y)	Brain metastasis (2 y, 4 mo), AWD (2 y, 7 mo)
Bilobectomy	pT1N1M0, IIA	Exon 19 (del)	Gefitinib (11 mo)	AWOD (11 mo)
Lobectomy	pT1N2M0, IIIA	Unknown	None	Brain metastasis (5 mo), AWD (2 y)
Left extrapleural pneumonectomy	pT4N2M0, IIIB	Exon 19 (del)	Gefitinib (3 mo)	Brain metastasis (3 mo), DWD (1 y, 7 mo)
Lobectomy	pT4N0M0, IIIB	Exon 19 (del) Exon 20 (T790M)	None	Metastasis in thorax (6 mo), AWD (10 mo)
Lobectomy	pT2N2M0, IIIA	Exon 21 (L858R) Exon 20 (T790M)	None	Metastasis in thorax (4 mo), DWD (1 y, 9 mo)
Lobectomy	pT2N0M0, IB	Unknown	Gefitinib	Unknown

the timing of surgery, and the role of adjuvant EGFR-TKI treatment should be also investigated in the future.

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Aortic dissection and rupture in adolescents after tetralogy of Fallot repair

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Aortic dissection in children and adolescents is rare, yet it is associated with high mortality. A recent article[1] describing 13 patients with aortic dissections operated between 1970 and 2000 reported an operative mortality of 38%. Progressive aortic root dilatation is a recognized feature of tetralogy of Fallot (TOF)[2,3] and generally managed conservatively. However, 2 recent reports of aortic dissection in patients with aortic aneurysm after TOF repair[4,5] together with the case presented reemphasize the fact that aortic root dilatation must be monitored closely in patients with TOF.