Induction chemoradiotherapy facilitates radical resection of T4 non–small cell lung cancer invading the spine

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Objective: We evaluated the outcome, long-term results, and factors affecting outcome of induction chemoradiotherapy followed by surgical resection for T4 non–small cell lung cancer invading the spine.

Methods: Retrospective analysis of 23 consecutive patients undergoing radical vertebral resection for non–small cell lung cancer invading the spine between 1996 and 2007 was performed. In most cases, induction chemoradiotherapy consisted of cisplatin and etoposide followed by 45 Gy of radiation. Surgical resection with vertebrectomy was performed en bloc in either a 1-stage or 2-stage operation. Survival was estimated by Kaplan–Meier techniques. The log–rank comparison was used to compare groups.

Results: There were 13 men and 10 women with a median age of 61 years (range 32–75). Twenty-two patients had induction chemoradiotherapy and 1 had induction chemotherapy alone. Vertebral resections included 6 total vertebrectomies, 15 hemivertebrectomies, and 2 partial vertebrectomies. Complete resection was achieved in 19 (83%) patients. Two (8.7%) patients died postoperatively. Pathologic complete response was observed in 10 (43%) patients. The 3-year survival was 58% (median follow-up, 34 months). Patients who achieved pathologic complete response or near complete response (viable tumor cells < 1%) demonstrated significantly better survival than those who did not (3-year survival, 92% vs 20%; $P = .006$).

Conclusion: Highly selected patients with lung cancer invading the spine can potentially be cured with induction chemoradiation therapy followed by radical en bloc resection of the tumor. A multidisciplinary operative strategy allows a significant chance of achieving complete resection in patients requiring multilevel hemivertebrectomy or total vertebrectomy and an appreciable cure rate.

Supplemental material is available online.

Surgical resection combined with chemoradiotherapy given either preoperatively or postoperatively has become the treatment of choice for locally advanced non–small cell lung cancer (NSCLC).¹ Advances in surgical techniques, postoperative care, and induction chemoradiotherapy allow aggressive resection with an acceptable mortality for patients with locally advanced stage III NSCLC that was once considered inoperable.²

Patients with vertebral body involvement historically have been considered to have unresectable disease.³ This

unfortunate group often has significant pain and neurologic sequelae, such as pathologic fracture with paralysis, despite best efforts with nonsurgical therapy. As innovative approaches have been developed since the late 1980s for vertebral resection and spinal reconstruction,^{4–6} low mortality and encouraging survival were reported in some series, leading to renewed hope for improvements in both survival and palliation through an aggressive combined modality approach.^{7–9}

However, the role of induction chemoradiotherapy in the treatment of T4 NSCLC invading the spine has yet to be clearly defined. The primary aim of our study was to delineate the impact of induction chemoradiotherapy on outcome in patients undergoing vertebrectomy for T4 NSCLC invading the spine. We also report our experience with a 2-stage approach for en bloc resection of tumors requiring 3-level or more hemivertebrectomy or multilevel total vertebrectomy.

PATIENTS AND METHODS

Pretreatment Staging

We retrospectively reviewed 23 consecutive patients who underwent surgery with vertebral body resection for NSCLC with curative intent between 1996 and 2007 at the University Health Network, University of Toronto. This study was approved by our institutional research ethics board at University Health Network, University of Toronto. Eligibility criteria for

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Abbreviations and Acronyms

CR	= complete response
CT	= computed tomography
MRI	= magnetic resonance imaging
NSCLC	= non-small cell lung cancer
R0	= complete resection
SWOG	= Southwest Oncology Group Trial

radical resection included the following: (1) pathologic diagnosis of NSCLC; (2) tumor invading the vertebral body on the basis of radiographic findings; (3) no evidence of mediastinal node involvement on mediastinoscopy; (4) no distant metastasis; and (5) no involvement of the spinal canal. Patients with radiologic evidence of brachial plexus involvement at C7 or higher or tumor involvement of the spinal cord or dura were excluded from surgical resection. Pretreatment evaluation included physical examination, standard laboratory tests, pulmonary function tests, chest radiography, computed tomography (CT scan) of the chest and abdomen, magnetic resonance imaging (MRI) of the chest and the spine, CT scan or MRI of the brain, examination with a flexible bronchoscope, and bone scan. Mediastinoscopy was performed on all patients to exclude mediastinal nodal disease.

Induction Therapy

The majority of the patients ($n = 18$) received induction chemoradiotherapy consisting of two cycles of cisplatin 50 mg/m² on days 1 and 8 and etoposide 50 mg/m² on days 1 to 5 administered concurrently with radiotherapy to a total dose of 45 Gy given in 1.8-Gy daily fractions. Three patients received the above cisplatin-etoposide chemotherapy regimen along with concurrent radiation to a total dose of 42, 65, and 66 Gy, respectively. The latter 2 patients receiving radiation of 65 and 66 Gy had extensive tumors (7 and 8 cm in size, respectively, and 4 levels of vertebrae involved); thus, the doses were designed to be maximized as curative doses in case the tumors were found to be unresectable. One was initially given three cycles of chemotherapy alone consisting of cisplatin and vinorelbine instead of combined chemoradiotherapy because of the very large size of the radiation field and concerns about radiation toxicity. Then, radiotherapy with a total dose of 24 Gy was given sequentially because of increasing tumor-related pain. One received chemotherapy alone with three cycles of cisplatin and gemcitabine.

The radiation field was planned with CT scan to include the primary tumor and the involved vertebra(e) with a margin. The mediastinal and hilar lymph nodes were not included in the radiation field, but the ipsilateral supraclavicular region was included in the radiotherapy field for superior sulcus tumors. Between 2 and 4 weeks after induction therapy, all patients were re-evaluated with CT scans and/or MRI of the chest and upper part of the abdomen. Brain CT scan or MRI was also performed. Four patients underwent postoperative chemotherapy with two cycles of cisplatin and etoposide. Postoperative adjuvant radiotherapy was not used.

Side effects seen during induction chemoradiotherapy included nausea (grade 1, $n = 3$; grade 2, $n = 3$), anorexia (grade 1 and 2, $n = 1$ each), fatigue (grade 1, $n = 2$; grade 2, $n = 1$), weight loss (grade 1, $n = 4$), neutropenia (grade 2, $n = 1$), esophagitis (grade 2, $n = 1$), and rash (grade 2, $n = 1$). No chemoradiotherapy-related mortality was observed.

Surgical Resection

The principles of resection were en bloc resection of the affected lung, chest wall, nerve roots, and vertebra with wide margins. The spinal resection was carried out through a posterolateral thoracotomy approach (anterolateral spinal approach) when the tumor involved the vertebral body anterior to the pedicle (anterior spinal elements only). After tumor resection, anterior or anterolateral spinal stabilization and instrumented fusion were per-

formed. Tumors involving the pedicle of the vertebra (anterior and posterior spinal elements) were approached through a combined posterior spinal approach and posterolateral thoracotomy (simultaneous or separate). Tumors involving T1 or with extensions to the subclavian vessels were approached anteriorly with or without resection of the proximal part of the clavicle.

Staged surgery was performed when resections were deemed difficult and long procedures were expected; mainly when multilevel (3 levels or more) hemivertebrectomies or total vertebrectomy was planned. The first stage (stage I) entailed a posterior spinal procedure. Multilevel instrumentation (including pedicle screw fixation and rod stabilization) spanning proximal and distal to the involved spine was placed on the side contralateral to the tumor. On the ipsilateral side, fixation implants only were placed above and below the tumor resection site. Posterior hemilaminectomies or complete laminectomies were performed where applicable at the level of the tumor. Ipsilateral nerve roots were ligated at their origin off the neural axis. Release of the necessary posterior soft tissue (disc, ligaments, and muscles) and bony (facet joints and transverse process) spinal elements, as well as partial posterior vertebral body osteotomies, was performed as required. Care was taken to preserve as much posterior paraspinal musculature as possible to maintain adequate soft tissue coverage of the spinal implants. At no point was the tumor exposed during this part of the procedure.

Approximately 1 to 2 weeks after the stage I operation, a lateral or anterior approach was performed with the patient in the lateral decubitus or supine position (stage II). After localization of the tumor, the chest wall was resected en bloc with the lobe without violating the tumor margins. The spinal resection was completed by performing osteotomy (from the anterior and/or posterior direction) of the vertebral body medial to the affected pedicle to obtain a clear spinal margin. Tumors invading a large portion of the vertebral body required complete vertebral body resection. The procedure of vertebral resection (total or hemivertebrectomy) was chosen on the basis of preoperative CT and MRI taken after induction therapy. After complete release of the involved portion of the spinal column from the thecal sac, the en bloc specimen of the lung, vertebral bodies, and the involved chest wall was removed (Figure 1, A). Any margins of concern (eg, perivertebral tissues) were checked by pathologic analysis of intraoperative frozen section in an attempt to achieve a complete (R0) resection whenever possible. After tumor resection, anterior and posterior spinal instrumentation and fusion were completed to allow for immediate mobilization of the patient (Figure 1, B). In the case of total vertebrectomy, a titanium mesh cage or a rib was used to replace the resected vertebral bodies.

Statistical Analysis

Data are presented as means $\pm$ standard deviation. Operative mortality was defined as death within the first 30 days after the operation or during the same hospitalization. Survival was measured from the date of the combined modality therapy started until death or the last date of follow-up (October 20, 2007). The survival curves were calculated with the Kaplan-Meier method, and comparisons between curves were performed by log-rank test. All data were analyzed with JMP, version 5.0 (SAS Institute, Inc, Cary, NC). Groups of continuous data were compared with the Wilcoxon rank sum test.

RESULTS**Patient Characteristics**

The preoperative patient characteristics and tumor histologic types are shown in Table 1. The median age was 61 years (range, 32–75 years). All cases were clinical stage IIIB disease (T4 N0). Poorly differentiated NSCLC could not be subclassified in 5 cases because of the lack of more specifically diagnostic features on preoperative cytology and the presence of extensive necrosis and lack of residual viable cells in the postoperative specimen. Most primary

FIGURE 1. A, Radiograph of a representative resected specimen. Right upper lobectomy with a 4-level total vertebrectomy was achieved en bloc. B, Post-operative posteroanterior and lateral chest x-ray films demonstrating successful anterior and posterior spinal instrumentation after 4-level total vertebrectomy.

tumors were in the upper lobe (87%) and were located in the superior sulcus (n = 17, 74%). The median size of the primary tumor was 7 cm (range, 4–11 cm). Regarding the extent of spinal involvement, all cases (n = 23) were categorized as Bilsky class D (ie, bony involvement of either vertebral body or posterior elements).¹⁰ Three patients were also entered in the Southwest Oncology Group (SWOG) 9416 (INT 0160) trial.¹¹

Surgery

The surgical characteristics are summarized in Table 2. A total of 14 (61%) patients underwent staged surgery. The surgical approach was generally a posterolateral thoracotomy along with a posterior midline incision (65%) or a hemi-clamshell incision combined with a posterior midline incision (26%). Two patients were operated on through a hemi-clamshell incision only. The average number of vertebrae resected was 3.5 in the staged surgery group and 2.5 in the remaining patients. All patients undergoing total vertebrectomies of more than 1 level had staged surgery. The staged surgery group included one 2-level, two 3-level, and one 4-level total vertebrectomy. There were 2 patients with the subclavian artery and vein resected and 8 patients with C8 or T1 or both C8 and T1 nerve roots resected because of subclavian vessel or brachial plexus tumor invasion. All but 1 patient undergoing vertebrectomy had en bloc resection of the tumor (96%).

Perioperative/Postoperative Course

The median duration of hospitalization was 23 days (range, 9–86 days) in the 1-stage surgery group and 24 days (17–171 days) in the staged surgery group (stage I + II). The mean operative time was 12.3 ± 4.0 hours in the 1-stage surgery group and 12.9 ± 3.8 hours for the second part of the staged surgery group. In the staged surgery group, the mean operative time for the first part of the operation was 6.4 ± 1.8 hours. The mean blood loss and blood transfusion during surgery were 2.7 ± 2.3 L and 1.6 ± 1.4 L, respec-

tively, in the 1-stage surgery group and 4.0 ± 1.9 L and 2.5 ± 1.4 L, respectively, for the second part of the staged surgery group. The mean blood loss for the first part of the staged surgery group was 1.2 ± 0.9 L.

A total of 11 (48%) patients had at least one major postoperative complication including pneumonia/respiratory failure in 7, bronchial kinking, vocal cord paralysis, spinal device dislocation, and bronchopleural fistula in 1 each. Two (8.7%) of the 11 patients died postoperatively because of pneumonia and a bronchopleural fistula.

The predicted value for vital capacity was significantly smaller in patients who had postoperative respiratory complication than in those with no complications (82% ± 13% vs 99% ± 13%, *P* = .02). The forced expiratory volume in 1 second and diffusing capacity for carbon monoxide were not significantly different (79% ± 19% vs 90% ± 12%, *P* = .2, and 56% ± 17% vs 79% ± 31%, *P* = .2, respectively).

Pathologic Findings

R0 resection was achieved in 19 (83%) patients. R1 resection was found in 4 patients. The residual site of tumor

TABLE 1. Patient characteristics

Characteristic	No. of patients
Sex	
Male/female	13/10
Tumor histology	
Adenocarcinoma	4
Squamous	11
Large cell	3
NSCLC	5
Tumor location	
Right upper	9
Right lower	2
Left upper	11
Left lower	1

NSCLC, Non-small cell lung cancer.

TABLE 2. Surgical characteristics

	One-stage (n = 9)	Staged (n = 14)
Superior sulcus tumor (%)	8 (89)	9 (64)
Type of approach*		
Posterolateral	5	10
Anterior	4	4
Type of lung resection		
Lobectomy	8	12
Wedge resection	1	1
Pneumonectomy	—	1
Type of vertebral resection		
Total ($\pm$ partial)	2	4
Hemi ($\pm$ partial)	5	10
Partial	2	—
No. of vertebra(e) resected		
One	1	—
Two	2	1
Three	4	7
Four	2	6

*Posterior spinal approach was added whenever necessary.

was the brachial plexus in 2 patients and the subclavian artery, the spinal dura, and the paravertebral tissue in 1 patient each. All 4 patients had a superior sulcus tumor with multiple vertebral body involvement: T1–3 in 2 patients and C7–T3 and T1–4 in 1 patient each. Postinduction pathologic stages in resected specimens were T0 N0 in 11 (48%) patients, T3 N0 in 1 (4%), T4 N0 in 9 (39%), and T4 N1 and T4 N2 in 1 patient each. Pathologic complete response (CR) was observed in 10 (43%) patients and minimal microscopic residual disease (viable tumor cells < 1% in a largely necrotic/fibrous tumor) was documented in 3 (13%). All 10 patients with pathologic CR had received concurrent chemoradiotherapy with cisplatin–etoposide and 45 Gy of radiation before surgery. A notable discrepancy was observed between postinduction radiographic and pathologic findings

(Figure 2). The 10 patients with pathologic CR demonstrated a postinduction residual mass involving vertebral bodies on CT or MRI scans (stable disease in 9 and partial response in 1).

Survival Analysis

The median follow-up period was 34 months (range, 7–105 months). The overall 1-year and 3-year survivals for all patients were 64% and 58%, respectively (Figure 3, A). The median survival of all patients was 47 months. Patients with R0 resection (n = 14) achieved 78% 1-year and 72% 3-year survival, whereas those with pathologic incomplete resection (n = 4) demonstrated 0% 1-year survival ($P = .004$; Figure 3, B). Patients with pathologic CR or minimal microscopic residual disease demonstrated significantly better survival than those with pathologic residual disease (median survival not reached vs 10 months; $P = .006$; Figure 4). The 3-year survival of patients with pathologic CR/minimal microscopic residual disease was 92%, whereas the 1-year survival was 25% in patients with residual disease in the resected tumors. Of the 6 patients with total vertebrectomy, 3 had residual disease in the resected specimen and died between 7 and 9 months after their treatment. The remaining 3 patients had pathologic CR and are alive without clinical and radiologic tumor recurrence 21, 82, and 105 months after their treatment, respectively. Other potential prognostic factors including sex, tumor size (≥ 7 cm vs < 7 cm), cell type (squamous cell carcinoma vs others), level of vertebral involvement (T1 or higher vs lower than T1 level), and total amount of red blood cell transfusion (≥ 2 L vs < 2 L) were not significant prognostic factors for survival after surgery.

Local tumor control after R0 resection was excellent with only one local recurrence (4%). Distant recurrence was observed in 3 (13%) patients, including lung (n = 2), bone

FIGURE 2. A, Computed tomographic scan demonstrating a tumor in the right upper lobe extending into the vertebral body. B, Signs of vertebral body invasion remained after induction chemoradiotherapy, but no viable tumor cells were observed in the resected specimen (pathologic CR).

FIGURE 3. A, Overall survival for all patients who underwent induction chemoradiotherapy followed by radical vertebrectomy (n = 23). B, Survival according to the completeness of resection (complete versus incomplete resection).

(n = 1), and adrenal gland (n = 1). All recurrent disease occurred within 1 year after surgery.

DISCUSSION

The current standard of care for locally advanced NSCLC is a combination of chemotherapy and radiotherapy, given either concurrently or subsequently.¹² However, there are some subsets of patients, in particular those with T4 N0–1 tumors, for whom surgery may have a vital role to play.¹ Our study clearly shows that induction chemoradiotherapy followed by en bloc radical resection and vertebrectomy is feasible and offers excellent local tumor control and promising long-term survival results. Rusch and associates¹¹ have recently reported the mature survival results of surgical resection preceded by induction chemoradiotherapy for T3–4 N0–1 superior sulcus NSCLC (SWOG 9416). The authors concluded that concurrent induction chemoradiotherapy

FIGURE 4. Survival according to the pathologic response in the resected specimen in patients with R0 resection (pathologic CR, n = 10; near CR*, n = 3; pathologic residual disease, n = 6). *Viable tumor cells less than 1% in a resected tumor.

was associated with high rates of R0 resection with 83 (94%) of 88 patients who underwent surgery achieving R0 resection. Pathologic CR or minimal microscopic residual disease was seen in 61 (56%) resected specimens. In our study, the pathologic CR (or minimal microscopic residual disease) rate was comparable (57%) in patients who underwent the same concurrent induction chemoradiotherapy regimen of cisplatin and etoposide. Given that pathologic CR is a crucial prognostic factor as shown both in SWOG 9416 and in our study, effective induction treatment is of importance in surgical candidates who have locally advanced NSCLC, including those tumors invading the vertebral body. However, T4 N2 disease is quite different from T4 N0–1 in prognosis. Patients with N2 and N3 disease in the SWOG series had 5-year survivals of only 13% and 15%. We carefully excluded N2 disease by mediastinoscopy before induction therapy in candidates for surgical resection. Some groups have reported innovative strategies of induction chemotherapy with hyperfractionated accelerated radiotherapy,^{13–17} induction platinum-based chemoradiotherapy combined with either third-generation^{15,17} or oral chemotherapeutic agents,¹⁸ or induction chemotherapy with concurrent dose-escalated radiotherapy¹⁹ for locally advanced NSCLC to obtain increased tumor response and improved survival (Table E1). Furthermore, improvements in dose-localization techniques such as intensity-modulated radiation therapy or image-guided radiation therapy may improve the local response rate as well as decrease radiation toxicity.²⁰

Our median survival of 47 months and 54% 3-year survival compare favorably with the results in patients with pathologically confirmed T4 N0–1 NSCLC who received definitive chemoradiotherapy *without surgery* (median survival, 20 months; 3-year survival, 22%) reported by Albain

TABLE 3. Surgical series of NSCLC undergoing vertebrectomy

Author	n	Vertebrectomy		Multilevel† (%)	Treatment protocol (No.)	R0 resection (%)	Survival (%)
		Total	Hemi*				
DeMeester ⁹	12	—	12	0 (0)	R → S (12)	92	42 (2 year)
Gandhi ⁸	17	7	10	3 (18)	S alone (1), R → S (1) S → R (6), C+R → S (3) S → C+R (6)	65	54 (2 year)
Grunenwald ⁷	19	4	15	3 (16)	S (8), R → S (2) C → S (5), C+R → S (4)	79	53 (2 year)
Fadel ²²	17‡	1	16	1 (6)	S → R (9), C → S → R (7) C+R → S → R (1)	77	39 (3 year)
Present series	23	6	17	4 (17)	C+R → S (22), C → S (1)	83	58 (3 year)

NSCLC, Non-small cell lung cancer; R, radiotherapy; S, surgery; C, chemotherapy; NS, not stated. *Partial vertebrectomy and transverses process resection included. †Number of cases with two or more total vertebrectomies. ‡All had direct tumor spread into the intervertebral foramina without spinal canal or vertebral body invasion.

and coworkers.²¹ The chemoradiotherapy protocol used in their study was the same as ours, in which chemotherapy consisted of two cycles of cisplatin and etoposide with 45 Gy of concurrent radiotherapy. In the absence of progressive disease, radiotherapy continued to a total dose of 61 Gy and two more cycles of chemotherapy were administered after completion of radiation.

Staged surgery is an integral part of our treatment strategy of en bloc vertebrectomy, especially in patients requiring a multilevel total vertebrectomy. We started using staged surgery in 2003 and since then have resected three or more vertebrae in 13 (93%) of 14 patients, of whom 4 received a multilevel total vertebrectomy. Inasmuch as the first-stage operation does not necessitate performing a thoracotomy, recovery from the operation is generally quite rapid, despite the blood loss related to the spinal procedures. Thus, we were able to perform the second part of the operation to complete the en bloc resection 1 week after the first-stage operation without encountering problematic adhesive changes at the site of operation. The longer operation time and greater blood loss seen in the staged surgery group in general reflected the more advanced cases that were selected for the staged procedures for en bloc resection. In our series, en bloc R0 tumor resection appeared to be critical inasmuch as favorable outcomes were obtained even in patients requiring multilevel total vertebrectomy when en bloc R0 resection was successfully performed. Outcomes of previously reported series of vertebral resection for NSCLC and ours are summarized in Table 3.

In our series, only 1 patient required reoperation for a spine-related complication (spinal device dislocation). Some have argued that preoperative radiotherapy adds little to the cure and may increase local tissue fragility^{9,22}; however, on the basis of our results and those of others,⁷ secure reconstruction can be achieved with appropriate anterior fixation and extended posterior fixation, both above and below the levels of resected vertebrae, even after induction chemoradiotherapy.

There are some limitations of this study. Inasmuch as this is a retrospective, nonrandomized, single-institutional study with highly selected patients over the past 10 years, a solid

conclusion cannot be drawn; however, a randomized, large-scale study is not realistic owing to the small numbers of such patients. In addition, formal quality-of-life assessment of these patients would better refine the roles of this aggressive treatment protocol in a group of patients who would otherwise have a dismal outcome, not only in terms of poor survival, but also significant pain and in many cases paralysis resulting from local tumor progression.

In conclusion, induction chemoradiotherapy followed by staged en bloc vertebral resection is a treatment option for selected patients with NSCLC invading the spine. The en bloc resection can be performed safely with a relatively low mortality rate. Although the short-term morbidity was high, most complications were manageable. The morbidity seems to be justifiable in view of the long-term results observed at our institution, although longer-term follow-up is required. However, we emphasize that this sort of treatment should only be undertaken by a dedicated team of thoracic and spinal surgeons in an institution that has the necessary postoperative support to manage the immediate postoperative complications. Inasmuch as pathologic CR is a strong indicator of favorable prognosis, refinements of induction therapy may be important in further improving outcomes in this group of patients in the future.

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TABLE E1. Pathologic complete response rate in selected recent induction chemoradiation protocols for patients with stage IIIB NSCLC

Author (y)	n*	Regimen	Pathologic CR† (%)
Eberhardt ¹³ (1998)	42 (8)	Cis/Eto with Hf-RT (45 Gy)	36
Grunenwald ¹⁴ (2001)	40 (6)	Cis/5FU/Vin with Hf-RT (42 Gy)	17
DeCamp ¹⁵ (2003)	27 (3)	Cis/Pac with Hf-RT (30 Gy)	11‡
Ichinose ¹⁸ (2003)	27 (4)	Cis/UFT with RT (40 Gy)	24
Trodella ¹⁶ (2004)	35 (30)	Carb or Cis/5FU with RT or Hf-RT (50.4 Gy)	29‡
Sonnet ¹⁹ (2004)	10 (4)	Platinum-based with RT (59.6-66.6 Gy)	30
Marra ¹⁷ (2007)	31 (4)	Cis/Eto or Cis/Pac with Hf-RT (45 Gy)	45§
Rusch ¹¹ (2007)	32 (32)	Cis/Eto with RT (45 Gy)	36§
Anraku (2008)	23 (23)	Cis/Eto with RT (42-66.6 Gy)	43

*(Cases of T4 N0, 1 in reported series.) CR, Complete response; *Cis*, cisplatin; *Carb*, carboplatin; *Eto*, etoposide; *Pac*, paclitaxel; *UFT*, oral uracil/tegafur; *5FU*, 5-fluorouracil; *Vin*, vinblastine; *RT*, radiotherapy; *Hf-RT*, hyperfractionated radiotherapy. †Percent in patients with surgical resection. ‡Clinical stage IIIA included. §Clinical stage IIB (T3) and IIIA included.