continued

Institution
Takasago Municipal Hospital
Tenri Hospital
The Cancer Institute Hospital of JFCR
The Jikei University Hospital
Tochigi Cancer Center
Toho University Omori Medical Center
Toho University Sakura Medical Center
Tohoku Kosai Hospital
Tohoku University Hospital
Tokai University Hachioji Hospital
Tokai University Hospital
Tokushima Red Cross Hospital
Tokushima University Hospital
Tokyo Medical and Dental University Hospital
Tokyo Medical University Ibaraki Medical Center
Tokyo Medical University Hospital
Tokyo Metropolitan Cancer and Infectious Center Komagome Hospital
Tokyo Metropolitan Health and Medical Corporation Toshima Hospital
Tokyo University Hospital
Tokyo Women's Medical University Hospital
Tokyo Women's Medical University Medical Center East
Tonan Hospital
Toranomon Hospital
Tottori Prefectural Central Hospital
Tottori University Hospital
Toyama Prefectural Central Hospital
Toyama University Hospital
Tsuchiura Kyodo Hospital
Tsukuba University Hospital
University Hospital, Kyoto Prefectural University of Medicine
University of Miyazaki Hospital
Yamagata Prefectural and Sakata Municipal Hospital Organization
Yamagata Prefectural Central Hospital
Yamagata Prefectural Shinjo Hospital
Yamagata University Hospital
Yamaguchi-ken Saiseikai Shimonoseki General Hospital
Yamaguchi University Hospital
Yamanashi Prefectural Central Hospital
Yamanashi University Hospital
Yao Municipal Hospital
Yatsu Hoken Hospital
Yokohama City Municipal Hospital
Yokohama City University Hospital
Yokohama City University Medical Center
Yuri General Hospital

(Total 237 institutions)

Patient background

Table 1 Age and gender

*Excluding 40 missing cases of gender

Age	Male	Female	Unknown	Cases (%)
~29	8	1	0	9 (0.2%)
30~39	10	4	0	14 (0.3%)
40~49	123	25	0	148 (3.3%)
50~59	842	139	0	981 (21.9%)
60~69	1535	226	1	1762 (39.4%)
70~79	1168	154	3	1325 (29.6%)
80~89	179	44	0	223 (5.0%)
90~	10	4	0	14 (0.3%)
Total	3875	597	4	4476
Missing	25	6	0	31

Table 11 Types of primary treatment

Treatments	Cases (%)
Surgery	2607 (57.7%)
Esophagectomy	2456 (54.3%)
Palliative	151 (3.3%)
Chemotherapy/Radiotherapy	1178 (26.1%)
Endoscopic treatment	477 (10.5%)
others	46 (1.0%)
None/Unknown	214 (4.7%)
Total	4522
Missing	25

Table 12 Tumor location

*** Excluding 293 treatment unknown, other, and missing cases of treatment types**

Location of tumor	Cases (%)
Cervical	204 (4.8%)
Upper thoracic	570 (13.4%)
Middle thoracic	1993 (46.9%)
Lower thoracic	1178 (27.7%)
Abdominal	195 (4.6%)
EG	35 (0.8%)
EG-Junction(E=G)	28 (0.7%)
Cardia (G)	3 (0.1%)
Others	0 (0.0%)
Unknown	41 (1.0%)
Total	4247
Missing	7

Table 15 Histologic types of biopsy specimens

*** Excluding 285 treatment unknown, other, and missing cases of treatment types**

Histologic types	Total (%)	
Not examined	39	(0.9%)
SCC	3891	(91.4%)
SCC	2360	(55.5%)
Well diff.	345	(8.1%)
Moderately diff.	882	(20.7%)
Poorly diff.	304	(7.1%)
Adenocarcinoma	155	(3.6%)
Undifferentiated	20	(0.5%)
Carcinosarcoma	13	(0.3%)
Malignant melanoma	8	(0.2%)
Other tumors	34	(0.8%)
Dysplasia	0	(0.0%)
Unknown	95	(2.2%)
Total	4255	
Missing	7	

Table 16 Depth of tumor invasion, cT (UICC TNM 6th)

*** Excluding 285 treatment unknown, other, and missing cases of treatment types**

cT	Total (%)	
cTX	16	(0.4%)
cT0	9	(0.2%)
cTis	89	(2.1%)
cT1	185	(4.4%)
cT1a	420	(9.9%)
cT1b	699	(16.4%)
cT2	542	(12.7%)
cT3	1635	(38.5%)
cT4	544	(12.8%)
Unknown	112	(2.6%)
Total	4252	
Missing	10	

Table 17 Lymph node metastasis, cN (UICC TNM 6th)

*** Excluding 285 treatment unknown, other, and missing cases of treatment types**

cN	Total (%)	
cNX	65	(1.5%)
cN0	1946	(45.8%)
cN1	2115	(49.7%)
Unknown	126	(3.0%)
Total	4252	
Missing	10	

Table 18 Distant metastasis, cM (UICC TNM 6th)

*** Excluding 285 treatment unknown, other, and missing cases of treatment types**

cM	Total (%)	
cMX	35	(0.8%)
cM0	3530	(83.0%)
cM1	152	(3.6%)
cM1a	108	(2.5%)
cM1b	333	(7.8%)
Unknown	94	(2.2%)
Total	4252	
Missing	10	

Table 20 Clinical stage (UICC TNM 6th)

*** Excluding 285 treatment unknown, other, and missing cases of treatment types**

cStage	Endoscopic treatment (%)		Chemotherapy and/or radiotherapy (%)		Surgery				Total (%)	
					Palliative surgery (%)		Esophagectomy (%)			
0	66	(13.9%)	4	(0.3%)	2	(1.3%)	13	(0.5%)	85	(2.0%)
I	357	(75.0%)	146	(12.4%)	26	(17.3%)	574	(23.4%)	1103	(25.9%)
IIA	1	(0.2%)	131	(11.1%)	28	(18.7%)	465	(19.0%)	625	(14.7%)
IIB	5	(1.1%)	82	(7.0%)	13	(8.7%)	291	(11.9%)	391	(9.2%)
III	5	(1.1%)	398	(33.9%)	55	(36.7%)	797	(32.5%)	1255	(29.5%)
IV	2	(0.4%)	101	(8.6%)	4	(2.7%)	33	(1.3%)	140	(3.3%)
IVA	1	(0.2%)	51	(4.3%)	3	(2.0%)	52	(2.1%)	107	(2.5%)
IVB	4	(0.8%)	173	(14.7%)	7	(4.7%)	131	(5.3%)	315	(7.4%)
Unknown	35	(7.4%)	89	(7.6%)	12	(8.0%)	95	(3.9%)	231	(5.4%)
Total	476		1175		150		2451		4252	
Missing	1		3		1		5		10	

II. Clinical results of patients treated endoscopically in 2005

Table 22 Treatment details in patients receiving endoscopy

Treatment details	Cases (%)	
EMR	266	(55.9%)
EMR + YAG laser / APC	6	(1.3%)
EMR + ESD	1	(0.2%)
ESD	181	(38.0%)
ESD + other treatment	1	(0.2%)
PDT	1	(0.2%)
PDT + Esophageal stent	1	(0.2%)
YAG laser / APC	2	(0.4%)
Esophageal stent	14	(2.9%)
Tracheal stent	0	(0.0%)
Esophageal stenting + tracheal stenting	2	(0.4%)
Others	1	(0.2%)
Total	476	
Missing	1	

EMR: endoscopic mucosal resection, ESD: endoscopic submucosaldissection, PDT:photodynamic therapy, YAG: yttrium aluminum garnet, APC: Argon plasma coagulation, MCT: microwave coagulation theraphy, RFA: Radiofrequency ablation

*** "Esophageal stenting + tracheal stenting + other (PEG)" case is included in "Esophageal stenting + tracheal stenting".**

Table 26 Complications of EMR/ESD

Complications of EMR/ESD	Cases (%)	
None	428	(94.1%)
Perforation	9	(2.0%)
Bleeding	0	(0.0%)
Mediastinitis	0	(0.0%)
Stenosis	13	(2.9%)
Perforation+Mediastinitis	0	(0.0%)
Perforation+Stenosis	0	(0.0%)
Perforation+Mediastinitis+Stenosis	0	(0.0%)
Others	5	(1.1%)
Unknown	0	(0.0%)
Total	455	
Missing	1	

Table 30 Depth of tumor invasion of EMR/ESD specimens

Complications of EMR/ESD	Cases (%)	
None	428	(94.1%)
Perforation	9	(2.0%)
Bleeding	0	(0.0%)
Mediastinitis	0	(0.0%)
Stenosis	13	(2.9%)
Perforation+Mediastinitis	0	(0.0%)
Perforation+Stenosis	0	(0.0%)
Perforation+Mediastinitis+Stenosis	0	(0.0%)
Others	5	(1.1%)
Unknown	0	(0.0%)
Total	455	
Missing	1	

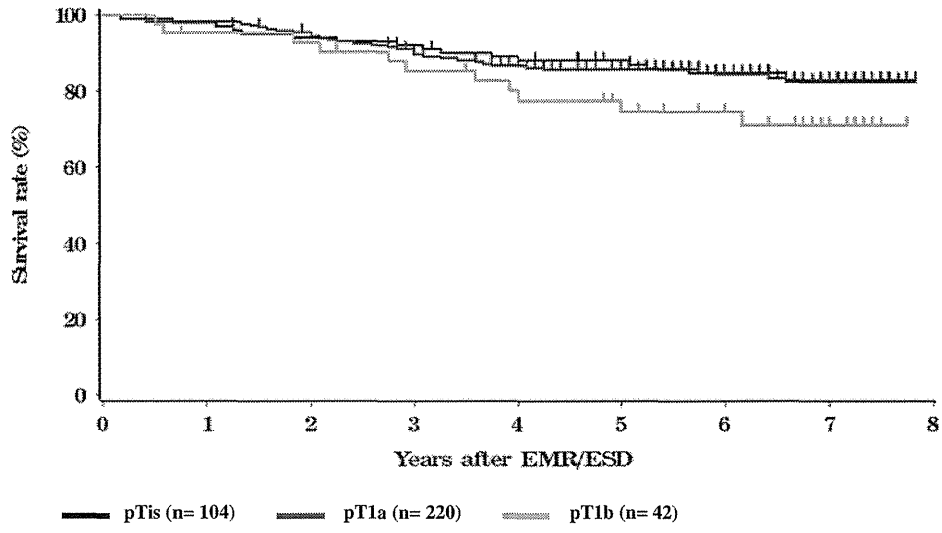

Fig. 3 Survival of patients treated by EMR/ESD in relation to the pathological depth of tumor invasion (pT), pTis (n = 104) pT1a (n = 220) pT1b (n = 42)

	Years after EMR/ESD							
	1	2	3	4	5	6	7	8
pTis	98.0%	94.1%	92.1%	89.1%	88.1%	84.7%	83.0%	83.0%
pT1a	98.2%	94.4%	91.1%	86.7%	85.7%	84.3%	82.5%	82.5%
pT1b	95.2%	92.8%	85.3%	80.2%	74.6%	74.6%	71.1%	71.1%

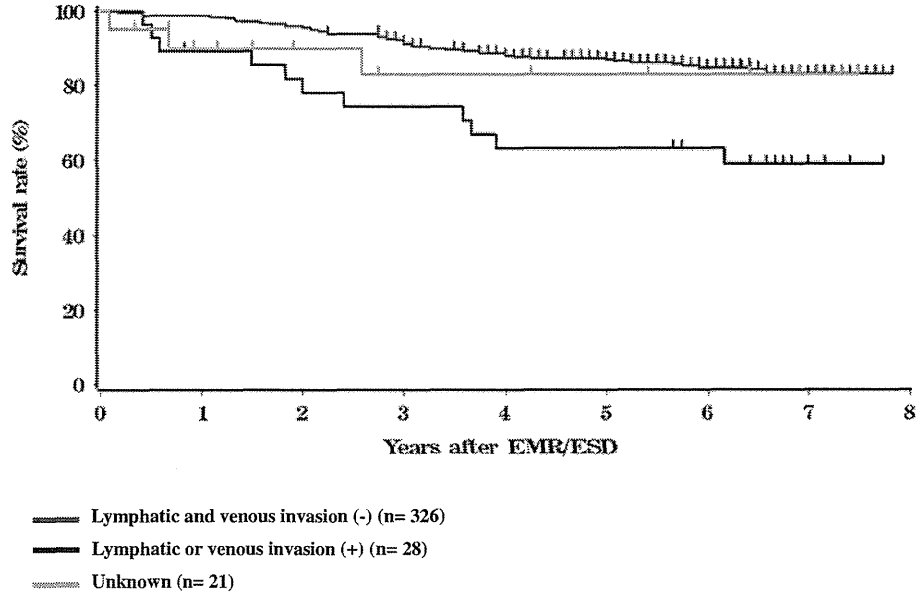

Fig. 4 Survival of patients treated by EMR/ESD in relation to the lymphatic or venous invasion, Lymphatic and venous invasion (−) (n = 326), Lymphatic or venous invasion (+) (n = 28), Unknown (n = 21)

	Years after EMR/ESD							
	1	2	3	4	5	6	7	8
Lymphatic and venous invasion (-)	98.8%	95.6%	92.2%	88.7%	86.9%	84.9%	83.1%	83.1%
Lymphatic or venous invasion (+)	89.3%	78.1%	74.4%	63.2%	63.2%	63.2%	59.0%	59.0%
Unknown	89.9%	89.9%	83.0%	83.0%	83.0%	83.0%	83.0%	83.0%

III. Clinical results in patients treated with chemotherapy and/or radiotherapy in 2005

Table 33 Dose of irradiation (non-surgically treated cases)

Dose of irradiation (Gy)	Radiotherapy				Palliative (%)		Recurrence (%)		Others (%)	Total (%)	
	alone (%)		with chemotherapy (%)								
0	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	0	(0.0%)
-29	3	(0.9%)	1	(1.4%)	9	(11.7%)	1	(7.7%)	0	14	(2.8%)
30-39	8	(2.4%)	1	(1.4%)	10	(13.0%)	0	(0.0%)	0	19	(3.8%)
40-49	13	(3.9%)	4	(5.6%)	5	(6.5%)	2	(15.4%)	0	24	(4.8%)
50-59	46	(13.7%)	5	(6.9%)	11	(14.3%)	3	(23.1%)	0	65	(13.1%)
60-69	261	(77.7%)	50	(69.4%)	32	(41.6%)	7	(53.8%)	0	350	(70.3%)
70-	5	(1.5%)	11	(15.3%)	10	(13.0%)	0	(0.0%)	0	26	(5.2%)
Total	336		72		77		13		0	498	
Median (min - max)	60 (1.8 - 70.2)		60 (22 - 70.2)		60 (2 - 76.8)		60 (20 - 67.6)		-	60 (1.8 - 70.6)	
Missing	5		0		8		0		1	14	

Table 34 Dose of irradiation (surgically treated cases)

Dose of irradiation (Gy)	Preope RT (%)		Postope RT (%)	
0	0	(0.0%)	0	(0.0%)
-29	3	(1.6%)	1	(1.6%)
30-39	61	(31.6%)	10	(15.9%)
40-49	106	(54.9%)	12	(19.0%)
50-59	7	(3.6%)	16	(25.4%)
60-69	14	(7.3%)	23	(36.5%)
70-	2	(1.0%)	1	(1.6%)
Total	193		63	
Median (min - max)	40 (20 - 70)		50 (20 - 70)	
Missing	10		7	

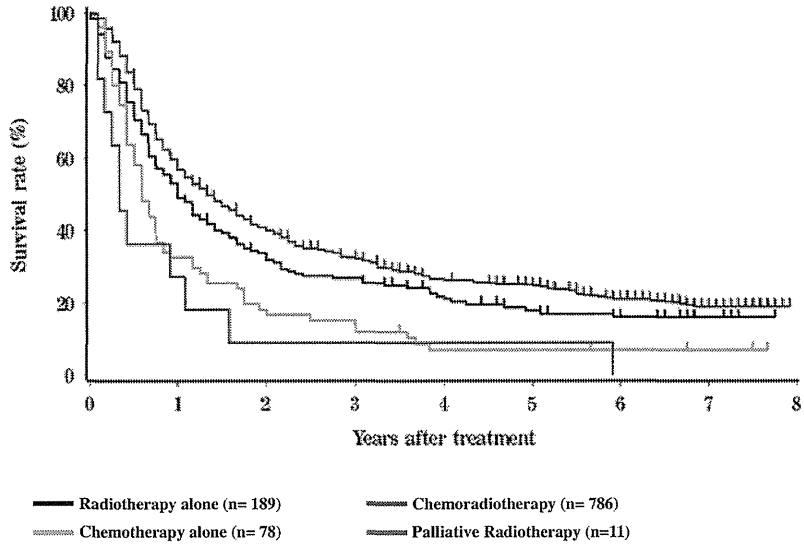

Fig. 5 Survival of patients treated by chemotherapy and/or radiotherapy, Radiotherapy alone (n = 189) Chemoradiotherapy (n = 786), Chemotherapy alone (n = 78) Palliative Radiotherapy (n = 11)

	Years after treatment							
	1	2	3	4	5	6	7	8
Radiotherapy alone	49.0%	31.9%	26.9%	21.9%	18.0%	16.1%	16.1%	16.1%
Chemoradiotherapy	56.8%	40.0%	32.6%	26.7%	24.9%	21.1%	19.0%	19.0%
Chemotherapy alone	32.6%	16.7%	13.7%	6.9%	6.9%	6.9%	6.9%	6.9%
Palliative Radiotherapy	27.3%	9.1%	-	-	-	-	-	-

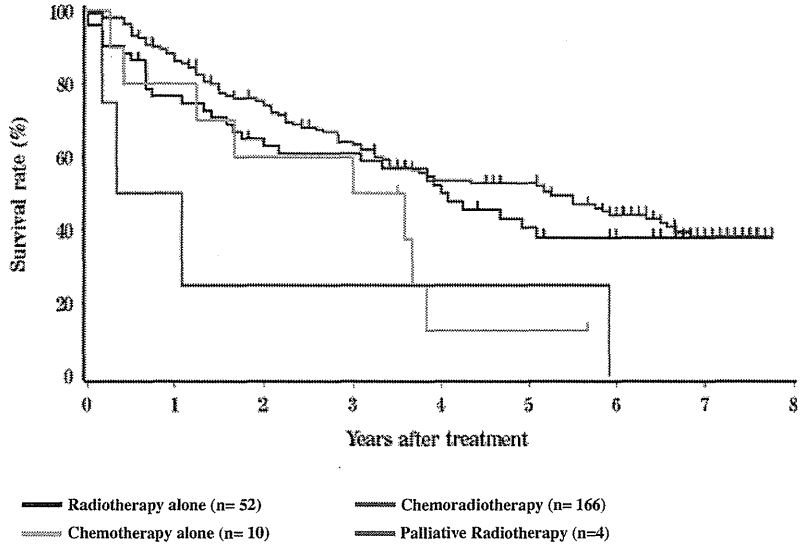

Fig. 6 Survival of patients treated by chemotherapy and/or radiotherapy (cStage I-IIA), Radiotherapy alone (n = 52) Chemoradiotherapy (n = 166), Chemotherapy alone (n = 10) Palliative Radiotherapy (n = 4)

	1	2	3	4	5	6	7	8
Radiotherapy alone	76.7%	62.9%	60.8%	52.2%	40.5%	38.0%	38.0%	38.0%
Chemoradiotherapy	86.4%	74.1%	64.0%	53.5%	52.7%	44.1%	38.1%	38.1%
Chemotherapy alone	80.0%	60.0%	50.0%	12.5%	12.5%	12.5%	-	-
Palliative Radiotherapy	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	-	-

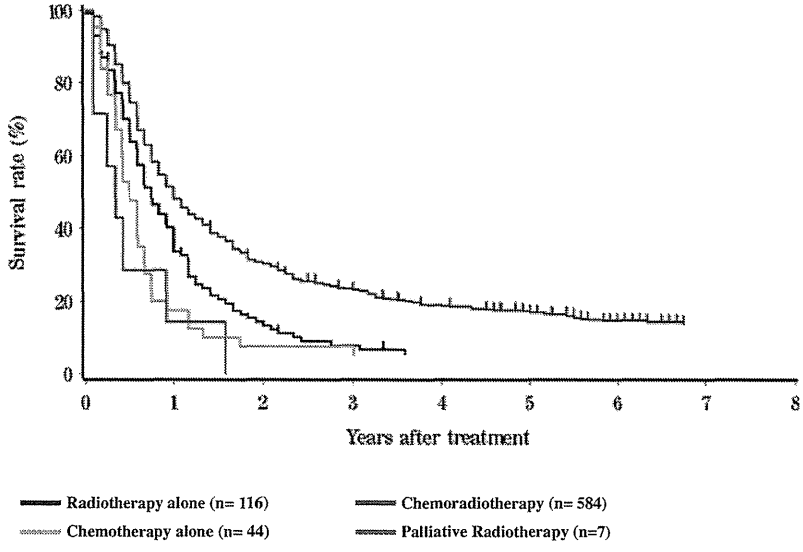

Fig. 7 Survival of patients treated by chemotherapy and/or radiotherapy (cStage IIB-IVB), Radiotherapy alone (n = 116) Chemoradiotherapy (n = 584), Chemotherapy alone (n = 44) Palliative Radiotherapy (n = 7)

	Years after treatment							
	1	2	3	4	5	6	7	8
Radiotherapy alone	33.6%	13.3%	7.9%	5.4%	5.4%	5.4%	5.4%	5.4%
Chemoradiotherapy	48.1%	30.4%	23.4%	18.9%	16.9%	14.6%	13.5%	-
Chemotherapy alone	17.6%	7.5%	7.5%	5.0%	5.0%	5.0%	5.0%	-
Palliative Radiotherapy	14.3%	0.0%	-	-	-	-	-	-

IV. Clinical results in patients treated by esophagectomy in 2005

Table 42 Tumor location

Locations	Cases (%)	
Cervical	89	(3.6%)
Upper thotacic	298	(12.2%)
Middle thoracic	1081	(44.2%)
Lower thoracic	765	(31.3%)
Abdominal	149	(6.1%)
EG	29	(1.2%)
EG-Junction (E=G)	22	(0.9%)
Unknown	10	(0.4%)
Total	2443	
Missing	13	

EG:
esophago-gastric

Table 43 Approaches to tumor resection

Approaches	Cases (%)	
Cervical approach	63	(2.6%)
Right thoracotomy	2023	(82.6%)
Left thoracotomy	45	(1.8%)
Left thoracoabdominal approach	52	(2.1%)
Laparotomy	101	(4.1%)
Transhiatal lower esophagectomy	65	(2.7%)
Transhiatal thoracic esophagectomy	32	(1.3%)
Sternotomy	7	(0.3%)
Others	53	(2.2%)
Unknown	8	(0.3%)
Total	2449	
Missing	7	

Table 44 Endoscopic surgery

Endoscopic surgery	Cases (%)	
None	1911	(79.0%)
Thoracoscopy-assisted	245	(10.1%)
Laparoscopy-assisted	97	(4.0%)
Thoracoscopy + Laparoscopy-assisted	136	(5.6%)
Mediastinoscopy-assisted	24	(1.0%)
Thoracoscopy + Mediastinoscopy-assisted	1	(0.0%)
Thoracoscopy + Laparoscopy + Mediastinoscopy-assisted	3	(0.1%)
Others	0	(0.0%)
Unknown	1	(0.0%)
Total	2418	
Missing	38	

Table 45 Fields of lymph node dissection according to the location of the tumor

*** Excluding pharynx and missing 20 cases of locations**

Locations	Cevical		Upper thoracic		Middle thoracic		Lower thoracic		Abdominal		EGJ		Total	
Region of lymphadenectomy	Cases (%)		Cases (%)		Cases (%)		Cases (%)		Cases (%)		Cases (%)		Cases (%)	
None	10	(11.4%)	10	(3.4%)	30	(2.8%)	28	(3.7%)	5	(3.3%)	0	(0.0%)	83	(3.4%)
C	27	(30.7%)	4	(1.4%)	3	(0.3%)	1	(0.1%)	0	(0.0%)	0	(0.0%)	35	(1.5%)
C+UM	14	(15.9%)	2	(0.7%)	2	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	18	(0.7%)
C+UM+MLM	4	(4.5%)	3	(1.0%)	12	(1.1%)	11	(1.4%)	0	(0.0%)	0	(0.0%)	30	(1.2%)
C+UM+MLM+A	21	(23.9%)	179	(61.1%)	553	(51.8%)	291	(38.3%)	7	(4.6%)	1	(0.7%)	1052	(43.7%)
C+UM+A	2	(2.3%)	1	(0.3%)	0	(0.0%)	3	(0.4%)	0	(0.0%)	0	(0.0%)	6	(0.2%)
C+MLM	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.1%)	0	(0.0%)	0	(0.0%)	1	(0.0%)
C+MLM+A	1	(1.1%)	0	(0.0%)	2	(0.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(0.1%)
C+A	4	(4.5%)	1	(0.3%)	4	(0.4%)	1	(0.1%)	0	(0.0%)	0	(0.0%)	10	(0.4%)
UM	0	(0.0%)	2	(0.7%)	9	(0.8%)	1	(0.1%)	0	(0.0%)	0	(0.0%)	12	(0.5%)
UM+MLM	0	(0.0%)	5	(1.7%)	13	(1.2%)	11	(1.4%)	0	(0.0%)	0	(0.0%)	29	(1.2%)
UM+MLM+A	3	(3.4%)	73	(24.9%)	378	(35.4%)	290	(38.2%)	48	(31.8%)	9	(6.0%)	801	(33.2%)
UM+A	0	(0.0%)	1	(0.3%)	3	(0.3%)	4	(0.5%)	2	(1.3%)	0	(0.0%)	10	(0.4%)
MLM	0	(0.0%)	0	(0.0%)	3	(0.3%)	6	(0.8%)	0	(0.0%)	2	(1.3%)	11	(0.5%)
MLM+A	0	(0.0%)	9	(3.1%)	39	(3.7%)	93	(12.2%)	67	(44.4%)	28	(18.5%)	236	(9.8%)
A	0	(0.0%)	2	(0.7%)	12	(1.1%)	18	(2.4%)	22	(14.6%)	10	(6.6%)	64	(2.7%)
Unknown	2	(2.3%)	1	(0.3%)	5	(0.5%)	1	(0.1%)	0	(0.0%)	0	(0.0%)	9	(0.4%)
Total	88		293		1068		760		151		50		2410	
Missing	1		5		13		5		1		1		26	

Table 47 Reconstruction route

Reconstruction route	Cases (%)	
None	41	(1.7%)
Subcutaneous	285	(11.7%)
Anterior mediastinal	868	(35.6%)
Intrathoracic	369	(15.1%)
Posterior mediastinal	828	(33.9%)
Cervical	23	(0.9%)
Others	18	(0.7%)
Unknown	9	(0.4%)
Total	2441	
Missing	15	

Table 48 Organs used for reconstruction

Organs used for reconstruction	Cases (%)	
None	50	(2.0%)
Whole stomach	101	(4.0%)
Gastric tube	2002	(78.5%)
Jejunum	118	(4.6%)
Free jejunum	37	(1.5%)
Colon	112	(4.4%)
Free colon	13	(0.5%)
Skin graft	1	(0.0%)
Others	114	(4.5%)
Unknown	3	(0.1%)
Total lesions	2551	
Total cases	2450	
Missing	6	

Table 55 Histological classification

Histological classification	Cases (%)	
Not examined	2	(0.1%)
SCC	2181	(89.8%)
SCC	370	(15.2%)
Well diff.	478	(19.7%)
Moderately diff.	957	(39.4%)
Poorly diff.	376	(15.5%)
Adenocarcinoma	81	(3.3%)
Barrett's adenocarcinoma	34	(1.4%)
Adenosquamous cell carcinoma	14	(0.6%)
(Co-existing)	1	(0.0%)
(Mucoepidermoid carcinoma)	1	(0.0%)
Adenoid cystic carcinoma	1	(0.0%)
Basaloid carcinoma	30	(1.2%)
Undiff. carcinoma (small cell)	9	(0.4%)
Undiff. carcinoma	6	(0.2%)
Other carcinoma	2	(0.1%)
Sarcoma	1	(0.0%)
Carcinosarcoma	19	(0.8%)
Malignant melanoma	8	(0.3%)
Dysplasia	1	(0.0%)
Other	18	(0.7%)
Unkown	20	(0.8%)
Total	2429	
Missing	27	

SCC: Squamous cell carcinoma

Table 56 Depth of tumor invasion

pT-category	Cases (%)	
pTX	9	(0.4%)
pT0	30	(1.2%)
pTis	40	(1.6%)
pT1a	209	(8.6%)
pT1b	547	(22.5%)
pT2	359	(14.8%)
pT3	1053	(43.4%)
pT4	158	(6.5%)
Other	0	(0.0%)
Unknown	23	(0.9%)
Total	2428	
Missing	28	

Table 58 Pathological grading of lymph node metastasis (JSED TNM 9th)

Lymph node metastasis	Cases (%)	
pT0	1230	(51.4%)
pT1	309	(12.9%)
pT2	495	(20.7%)
pT3	179	(7.5%)
pT4	143	(6.0%)
Unknown	39	(1.6%)
Total	2395	
Missing	61	

Table 59 Numbers of the metastatic nodes

Numbers of lymph node metastasis	Cases (%)	
0	1059	(44.2%)
1-2	629	(26.3%)
3-6	455	(19.0%)
7-	252	(10.5%)
Total	2395	
Missing	61	

Table 60 Pathological findings of distant organ metastasis

Distant metastasias (M)	Cases (%)	
MX	26	(1.1%)
M0	2319	(96.6%)
M1	56	(2.3%)
Total	2401	
Missing	7	

Table 61 Residual tumor

Residual tumor (R)	Cases (%)	
RX	172	(7.1%)
R0	2002	(83.0%)
R1	137	(5.7%)
R2	102	(4.2%)
Total	2413	
Missing	43	

Table 72 Causes of death

*** As of August 31, 2010**

Cause of death	Cases (%)
Death due to recurrence	817 (72.2%)
Death due to other cancer	53 (4.7%)
Death due to other disease (rec+)	23 (2.0%)
Death due to other disease (rec-)	121 (10.7%)
Death due to other disease (rec?)	4 (0.4%)
Operative death*	32 (2.8%)
Postoperative hospital death**	41 (3.6%)
Unknown	41 (3.6%)
Total of death cases	1132
Missing	8

rec: recurrence

*** Death within 30 days, **Death after 30 days**

Follow-up period (years)	
Median (min - max)	2.75 (0.00 - 7.41)

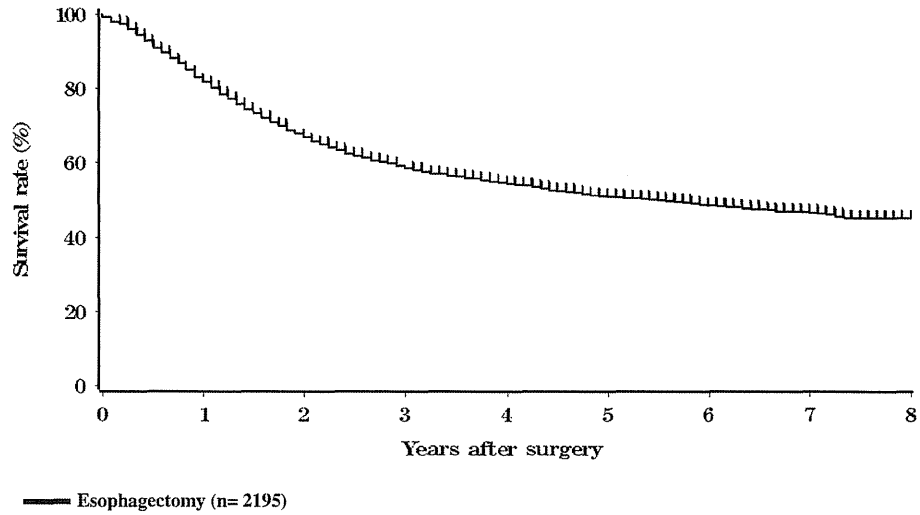

Fig. 8 Survival of patients treated by esophagectomy

	Years after surgery							
	1	2	3	4	5	6	7	8
Esophagectomy	**81.9%**	**67.0%**	**59.2%**	**54.8%**	**50.9%**	**48.7%**	**46.7%**	**45.2%**

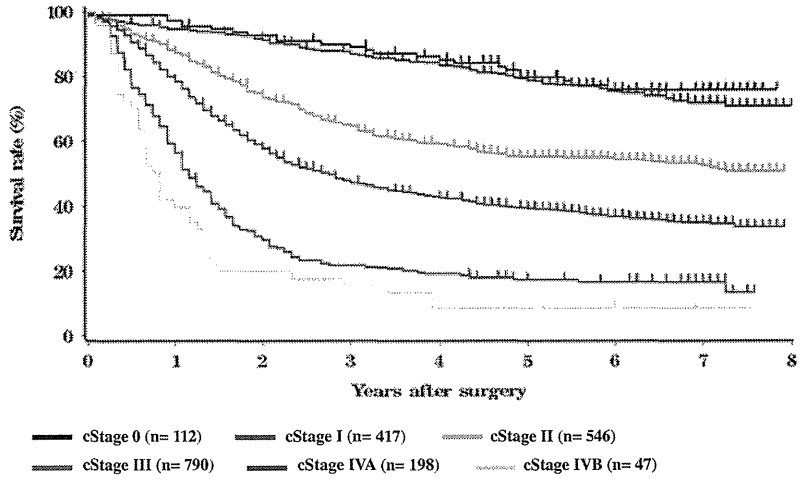

Fig. 9 Survival of patients treated by esophagectomy in relation to clinical stage (JSED TNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
cStage 0	97.3%	92.7%	89.0%	86.1%	79.8%	75.9%	75.9%	75.9%
cStage I	94.7%	91.2%	87.7%	84.4%	78.9%	75.2%	72.0%	71.0%
cStage II	87.4%	73.8%	65.1%	59.4%	55.3%	54.6%	52.6%	50.7%
cStage III	78.4%	57.9%	48.0%	42.9%	39.4%	36.7%	34.9%	33.5%
cStage IVA	56.5%	29.7%	21.7%	19.1%	17.4%	16.7%	16.7%	13.3%
cStage IVB	39.5%	19.7%	15.3%	8.8%	8.8%	8.8%	8.8%	-

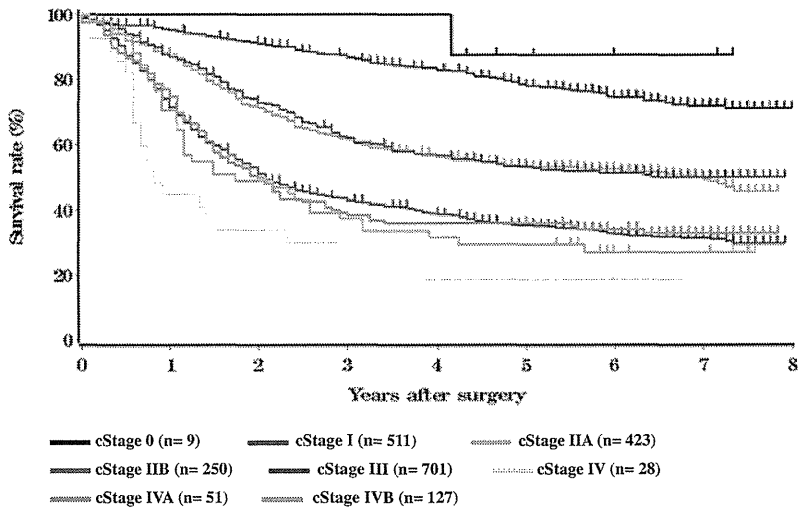

Fig. 10 Survival of patients treated by esophagectomy in relation to clinical stage (UICC TNM 6th)

	Years after surgery							
	1	2	3	4	5	6	7	8
cStage 0	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%
cStage I	95.3%	91.0%	87.3%	83.6%	78.1%	74.5%	71.9%	71.1%
cStage IIA	87.8%	71.4%	61.9%	57.1%	53.2%	52.6%	49.5%	45.6%
cStage IIB	87.0%	72.9%	62.4%	56.9%	53.3%	51.4%	50.0%	-
cStage III	71.6%	51.2%	43.5%	38.9%	35.4%	32.7%	31.5%	29.7%
cStage IV	44.7%	33.5%	26.1%	18.6%	18.6%	18.6%	-	-
cStage IVA	70.6%	49.0%	37.3%	31.4%	29.4%	27.0%	27.0%	-
cStage IVB	74.6%	49.8%	39.2%	35.9%	35.9%	34.1%	32.8%	-

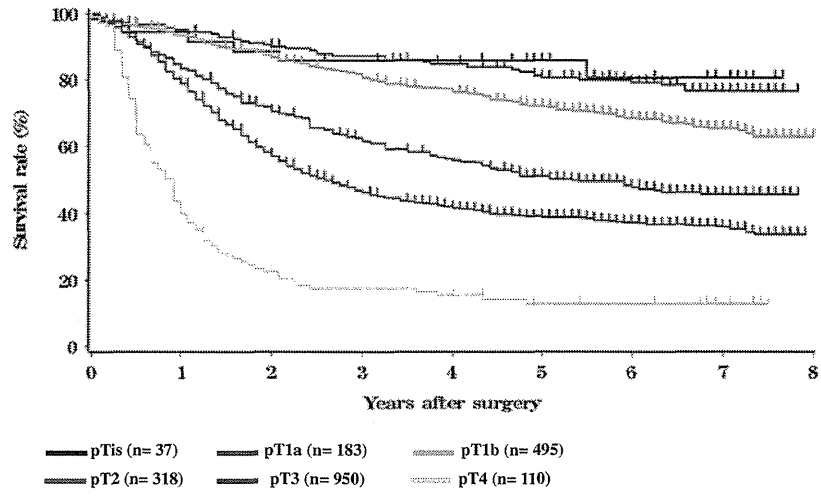

Fig. 11 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion: pT (JSED TNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	94.4%	88.6%	85.7%	85.7%	85.7%	80.6%	80.6%	-
pT1a	95.1%	90.0%	87.2%	84.9%	80.7%	79.3%	76.6%	76.6%
pT1b	93.5%	86.8%	81.5%	77.4%	71.9%	68.6%	65.5%	63.0%
pT2	83.5%	70.6%	62.7%	56.3%	51.1%	47.9%	45.8%	-
pT3	78.9%	57.2%	47.0%	42.1%	39.0%	37.3%	35.9%	33.8%
pT4	39.9%	22.5%	17.4%	15.3%	13.0%	13.0%	13.0%	-

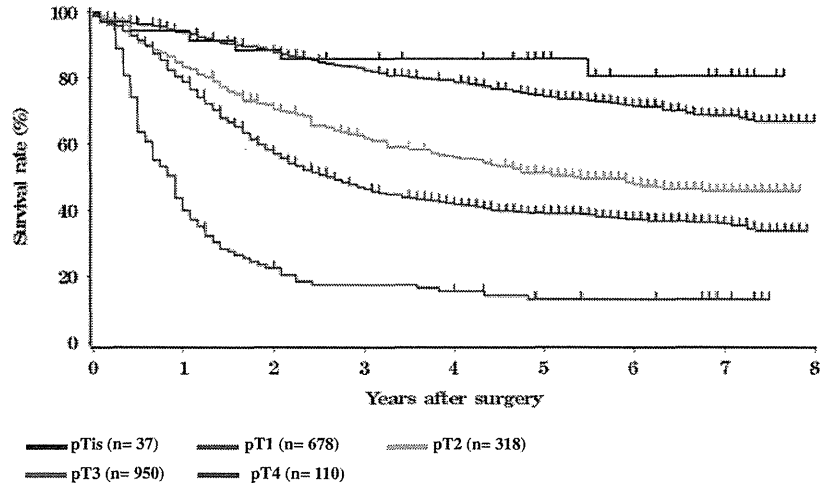

Fig. 12 Survival of patients treated by esophagectomy in relation to the depth of tumor invasion: pT (UICC TNM 6th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	94.4%	88.6%	85.7%	85.7%	85.7%	80.6%	80.6%	-
pT1	93.9%	87.7%	83.0%	79.5%	74.3%	71.5%	68.5%	66.7%
pT2	83.5%	70.6%	62.7%	56.3%	51.1%	47.9%	45.8%	-
pT3	78.9%	57.2%	47.0%	42.1%	39.0%	37.3%	35.9%	33.8%
pT4	39.9%	22.5%	17.4%	15.3%	13.0%	13.0%	13.0%	-

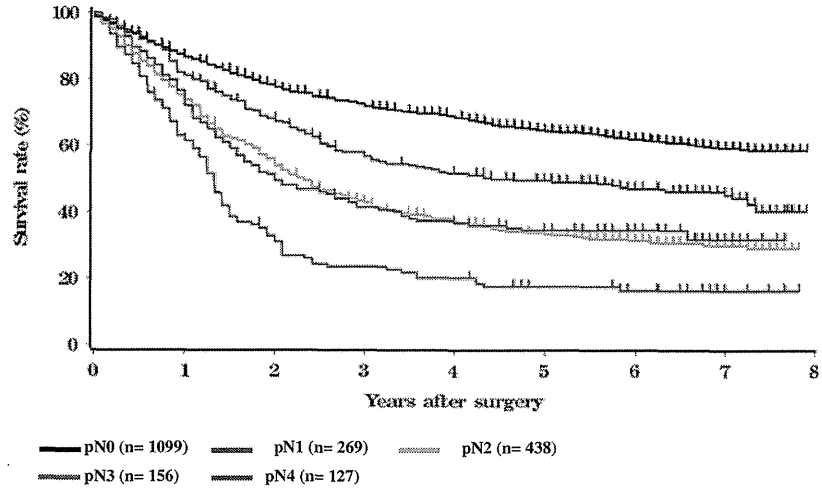

Fig. 13 Survival of patients treated by esophagectomy in relation to lymph node metastasis: pN (JSED TNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	86.8%	77.7%	72.6%	69.1%	64.6%	62.0%	59.4%	58.7%
pN1	81.3%	67.7%	58.2%	51.7%	49.6%	47.0%	45.3%	40.2%
pN2	74.1%	54.0%	43.6%	37.9%	33.5%	31.4%	30.0%	29.1%
pN3	72.1%	49.4%	41.4%	37.4%	34.5%	34.5%	31.9%	31.9%
pN4	61.5%	31.0%	23.5%	20.1%	17.5%	16.4%	16.4%	16.4%

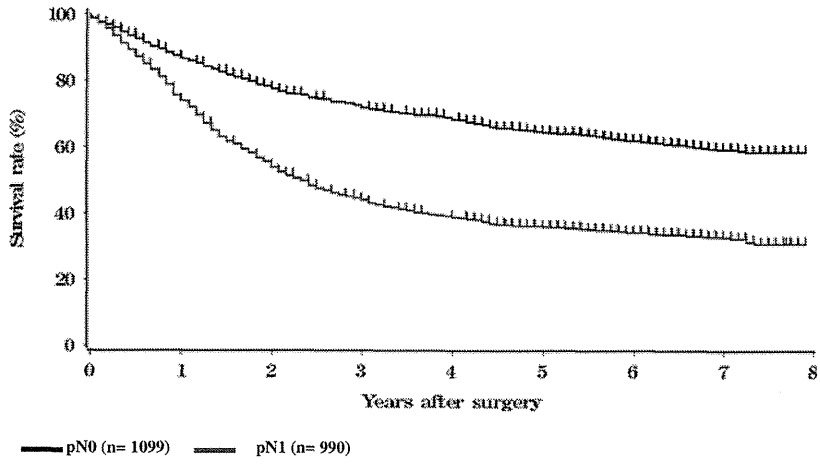

Fig. 14 Survival of patients treated by esophagectomy in relation to lymph node metastasis: pN (UICC TNM 6th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	86.8%	77.7%	72.6%	69.1%	64.6%	62.0%	59.4%	58.7%
pN1	74.1%	54.1%	44.6%	39.3%	36.0%	34.2%	32.7%	30.8%

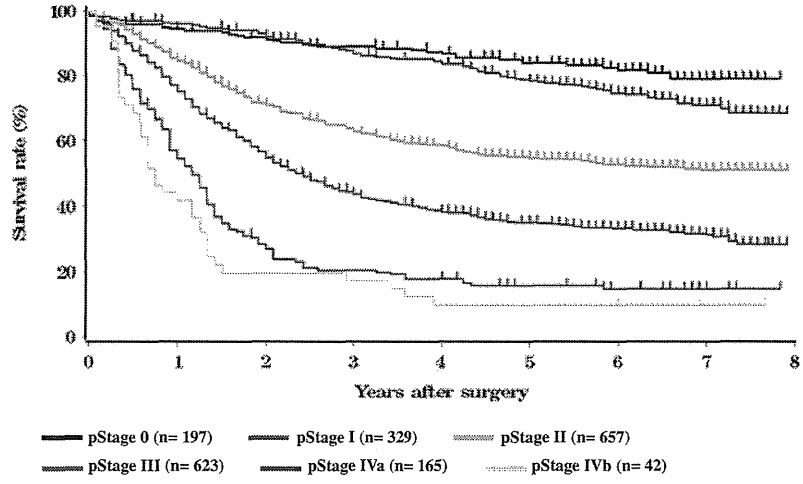

Fig. 15 Survival of patients treated by esophagectomy in relation to pathological stage (JSED TNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	94.4%	91.2%	89.0%	87.3%	83.8%	81.7%	79.0%	79.0%
pStage I	96.0%	91.9%	87.7%	84.5%	78.4%	74.6%	71.0%	68.5%
pStage II	84.6%	71.1%	63.6%	58.7%	54.7%	52.7%	51.0%	51.0%
pStage III	75.1%	54.7%	44.3%	38.7%	34.9%	33.2%	31.2%	28.2%
pStage IVa	54.6%	27.0%	20.4%	17.8%	15.6%	14.7%	14.7%	14.7%
pStage IVb	41.5%	19.5%	17.1%	9.8%	9.8%	9.8%	9.8%	-

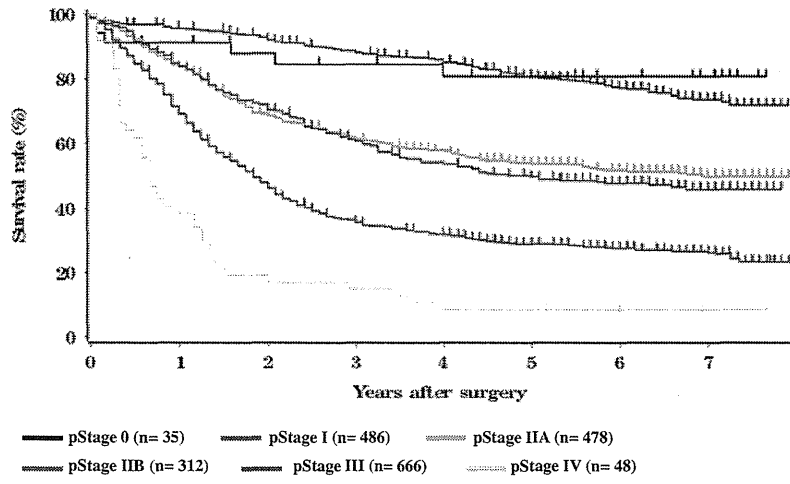

Fig. 16 Survival of patients treated by esophagectomy in relation to pathological stage (UICC TNM 6th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	91.3%	87.9%	84.5%	84.5%	80.8%	80.8%	80.8%	80.8%
pStage I	95.6%	92.0%	88.8%	85.9%	80.7%	77.2%	73.7%	71.9%
pStage IIA	83.7%	68.9%	62.0%	58.0%	53.8%	51.9%	50.1%	50.1%
pStage IIB	83.9%	70.8%	61.5%	54.4%	49.8%	47.8%	45.9%	45.9%
pStage III	69.2%	46.2%	36.5%	32.0%	29.1%	27.6%	26.3%	23.4%
pStage IV	38.4%	17.1%	14.9%	8.5%	8.5%	8.5%	8.5%	-

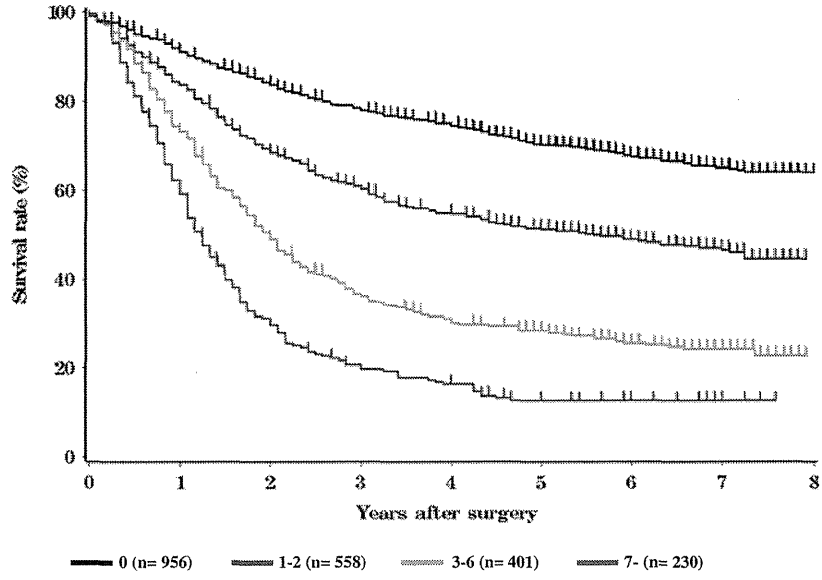

Fig. 17 Survival of patients treated by esophagectomy in relation to number of metastatic node

	Years after surgery							
	1	2	3	4	5	6	7	8
0	91.0%	83.7%	78.4%	75.1%	70.3%	67.7%	65.1%	64.0%
1-2	83.7%	68.5%	60.9%	54.9%	51.3%	48.9%	46.6%	44.5%
3-6	73.2%	48.9%	36.6%	30.9%	28.4%	25.5%	24.2%	22.7%
7-	59.2%	29.6%	20.8%	16.3%	12.6%	12.6%	12.6%	12.6%

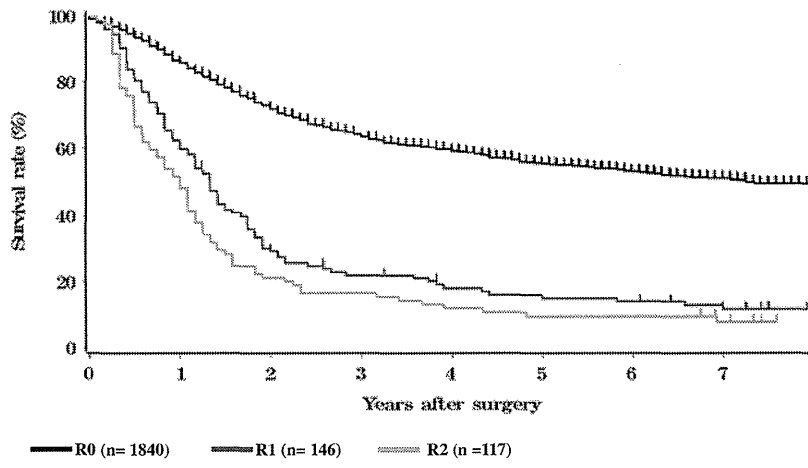

Fig. 18 Survival of patients treated by esophagectomy in relation to residual tumor

	Years after surgery							
	1	2	3	4	5	6	7	8
R0	85.8%	72.7%	64.2%	59.1%	56.1%	53.8%	49.0%	46.8%
R1	58.1%	34.4%	24.6%	22.3%	17.2%	15.4%	14.3%	14.3%
R2	43.5%	14.2%	7.1%	6.2%	5.3%	5.3%	4.4%	-

Radiotherapy for Postoperative Thoracic Lymph Node Recurrence of Non–Small-Cell Lung Cancer Provides Better Outcomes If the Disease Is Asymptomatic and a Single-Station Involvement

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Objective: Thoracic lymph node recurrence after complete resection is common in non–small-cell lung cancer but it mostly occurs along with distant metastases. The recurrent disease might be localized and curative intent radiation therapy is the treatment of choice if no evidence of hematogenous metastasis is observed. We sought to describe the outcomes of thoracic radiotherapy for thoracic lymph node recurrences.

Methods: Fifty patients who had developed thoracic lymph node recurrence after complete resection received curative intent radiotherapy between 1997 and 2009. The clinical endpoints included the tumor response, overall survival, progression-free survival, locoregional recurrence within the irradiated field, and any other recurrence.

Results: The planned total radiotherapy was completed in 49 patients with minor toxicity. The median follow-up time after radiotherapy was 41 (19–98) months among the survivors. The response to treatment was complete response in 65%, partial response in 24%, and progressive disease in 10% of the evaluated patients. The median overall survival after radiotherapy was 37.3 months. The 5-year overall survival, progression-free survival, and local control rate were 36.1%, 22.2%, and 61.1%, respectively. A multivariate analysis revealed that the absence of symptoms and the involvement of a single lymph node station were significant factors associated with a better overall survival.

Conclusions: Radiation therapy for thoracic lymph node recurrence after complete resection is safe and provides acceptable disease control. This treatment provides a better outcome if the disease is asymptomatic and has a single-station involvement. Early detection of the recurrence may thus improve the effectiveness of this treatment.

Key Words: Radiotherapy, Lymph node recurrence, Non–small-cell lung cancer.

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Disclosure: The authors declare no conflict of interest.

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Recurrence after surgery is common in patients with non–small-cell lung cancer (NSCLC). Once the disease has relapsed after surgery, it is seldom curable and the median survival time after recurrence is estimated to be 8.1 to 18.7 months.[1–3] Most recurrences occur in multiple sites including distant organs, thus chemotherapy is commonly used for this systemic state of the disease.[4]

Thoracic lymph node recurrence is one of the exceptions when there is no evidence of hematogenous spreading of the disease. The recurrent disease might be still localized in these patients and curative intent radiation therapy is the treatment of choice.[5] However, the efficacy and feasibility of radiotherapy for thoracic lymph node recurrence after a complete resection have not yet been clearly described. We retrospectively reviewed our experience to determine (1) progression-free survival, patterns of failure, and local control, (2) overall survival and associated factors, and (3) treatment compliance and toxicity.

PATIENTS AND METHODS

Patients

This study conducted a retrospective review of 1553 patients who underwent complete resection for NSCLC at the Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan, from January 1997 to December 2009. The ethics committee gave its approval for the publication of this retrospective study. The institutional prospective database of the general thoracic department included clinicopathological variables at surgery and the postoperative clinical course. The inclusion criteria for this study were patients with lymph node recurrence as the initial recurrence, which included intrathoracic lymph nodes and supraclavicular lymph nodes and that received radiation therapy for the recurrence. Patients with any other recurrence except the thoracic lymph nodes were excluded. The method how the patients were selected from the database was shown in a CONSORT chart (Fig. 1). Finally, we identified 50 patients who received radiotherapy for thoracic lymph node recurrence. The characteristics of these patients are summarized in Table 1. There were 17 patients with thoracic lymph node recurrence who did not receive radiotherapy.

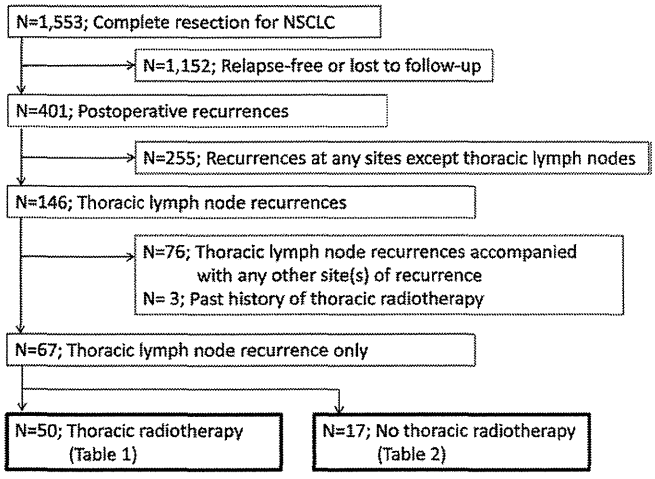

FIGURE 1. A flow chart of the patient selection. NSCLC, non–small-cell lung cancer.

The follow-up protocol for postoperative patients at this institution included a physical examination, chest radiograph, and blood testing including the value of carcinoembryonic antigen (CEA) every 3 to 6 months, and chest computed tomography (CT) every 6 to 12 months for at least 5 years. If patients were suspected of having developed recurrent disease, they were instructed to undergo systemic examinations including upper abdominal CT or abdominal echography, brain magnetic resonance imaging, and bone scintigraphy or ^{18}F-fluorodeoxy glucose-positron emission tomography (FDG-PET) before determining the treatment strategy. After undergoing thoracic radiotherapy, the patients were recommended to have more follow-up visits (every 1–3 months during the first 3 years) by surgeons and/or radiation oncologists. Six patients received concurrent systemic intravenous chemotherapy with radiotherapy.

Diagnosis of Lymph Node Recurrence

The diagnosis and status of lymph node recurrence of the patients who received radiotherapy are summarized in Table 1 (n = 50). The diagnosis of lymph node recurrence was based on the radiological findings of chest CT, FDG-PET, physiological examination, the value of CEA, and/or bronchoscopic sampling for cytology. Among 50 eligible patients, the cytological evidence was obtained in 10 patients (20%). Swollen lymph nodes exhibited significantly increased standard uptake values on PET scans in 31 patients (62%), and growing lymph nodes detected on at least two consecutive CT scans were observed in nine patients (18%). In these patients, radiotherapy was commenced without conducting further interventional examinations to obtain cytological evidence because lymph node recurrence was apparent on the radiological findings. The status and the treatment of recurrent diseases of the patients who did not receive radiotherapy are summarized in Table 2 (n = 17). There were more symptomatic diseases, more N3 level recurrences, and more multistation involvements in this group.

Protocol of Radiotherapy

The patients were treated using three-dimensional conformal techniques using a CT-based planning system (Eclipse; Varian Medical Systems, Palo Alto, CA). The gross tumor volume (GTV) was defined based on the assessment of the involved nodal region in the CT images. In addition, lymph nodes that were positive for FDG accumulation by PET/CT were included in the GTV, even if their sizes were within the normal limits on CT. The clinical target volume was defined as the GTV plus a 5-mm margin. Two different radiotherapeutic approaches, regional nodal irradiation and involved-field irradiation, were used in this study. Regional nodal irradiation covered two or more areas of five thoracic lymph node areas (right- and left-hilar areas, superior mediastinum area, supraclavicular area, and subcarinal area) in the GTV whether or not involved lymph nodes were present in the stations, whereas the involved-field irradiation covered only metastatic lymph nodes regardless of the anatomical compartment of thoracic lymph node areas. Radiotherapy was not systematically performed according to the predetermined protocol for all cases. Basically, a regional nodal irradiation approach was considered the first choice for all patients, but if the coverage of all involved stations elevated normal tissue toxicity or the patients had impaired medical conditions, the involved-field irradiation technique was applied. The treatment approach was determined on an individual basis by the experienced radiation oncologist (Table 1). Planning treatment volume denoted the clinical target volume and 5 to 15 mm margins for geometric uncertainties and respiratory motion. The prescribed dose was calculated with a heterogeneous dose calculation algorithm (pencil beam convolution or anisotropic analytical algorithm). Conventional fractionation was used (2–3 Gy per fraction) and the preplanned radiation dose ranged from 60 to 66 Gy in 43 patients. In four patients, the dose was reduced to 50 Gy because of the radiation field and/or patient's medical condition. In three patients, the dose was increased up to 70 to 84 Gy. Treatment was delivered using 6- or 10-MV photons of the linear accelerator (Clinac 2100C/23EX; Varian Medical systems). Dose prescription was defined according to International Commission on Radiation Units and Measurements recommendations.

Clinical Endpoints

Clinical endpoints after radiotherapy included the overall survival, progression-free survival, tumor response, and locoregional recurrence within the irradiated field and any other recurrence. All responses were evaluated 3 to 6 months after the completion of radiotherapy based on follow-up CT and/or PET scan. Complete response (CR) was defined as the shrinking of metastatic nodes to normal size (the longest diameter was <10 mm) on chest CT without significant accumulation of FDG on PET. The value of CEA was also required to be within the normal limit if it was elevated before the radiotherapy. Partial response required more than 30% reduction of the longest diameter. Progressive disease was defined as increase of more than 20% of the longest diameter and/or progression of any other recurrent disease. Local tumor recurrence was defined as progressive abnormal CT images within the irradiated field during the follow-up period. The time of recurrence

TABLE 1. Patient Characteristics, the Diagnosis, and Status of Lymph Node Recurrence, and Treatment Protocol of Thoracic Radiotherapy

Variables	N = 50	Univariate Analysis for Overall Survival, *p*
Age at LN recurrence, years old		0.6915 (≤67 vs. >68)
Median (range)	68 (48–84)	
Sex (male/female)	42/8	0.4085
Smoking status (nonsmoker/smoker)	11/39	0.9443
Primary site		
Right/left	32/18	0.5459
Upper or middle/lower	31/19	0.7960
Surgery		
Limited resection (wedge/segmentectomy)	6 (3/3)	0.5875
Standard surgery (lobectomy/bilobectomy/pneumonectomy)	44 (39/4/1)	
Histology (adenoca/squamous/others)	21/27/2	0.5706
Stage[a] at surgery		0.5723 (I or II vs. III)
IA/IB/IIA/IIB/IIIA	11/3/10/0/26	
Disease-free interval after surgery, days		0.2965 (≤365 vs. >365)
Median	324	
Range	86–3088	
Diagnostic procedure		
Patho- or cytological examination	10	
PET/CT	31	
CT (+symptom or elevated CEA)	9	
Number of stations (single/multiple)	30/20	0.0457
Site of LN recurrence		0.2331 (N1 vs. N2/N3)
N1 level		
Ip–hilar only	10	
N2 level		
Upper med. (+ip–hilar)	19	
Lower med. (+ip–hilar)	5	
Upper and lower med. (+ip–hilar)	4	
N3 level		
SC (+upper or lower med.)	10	
Cl–hilar and upper med.	2	
Symptoms at recurrence ([b]present/absent)	13/37	0.0017
Maximum diameter of involved LN (mm)		0.4784
20 or smaller/21 or larger	26/24	
Radiation approach		0.3853
Regional nodal/involved-field	23/27	
Radiation dose (Gy)		0.4325 (≤60 Gy vs. >60 Gy
50~59/60~69/70~	4/43/3	
Concurrent chemotherapy		0.6185
Yes/no	6/54	

[a]The stages were described according to the 7th edition.
[b]Details are cough in seven patients, sputum production in five patients, bloody sputum in two patients, breathlessness in two patients, and hoarseness in two patients.
LN, lymph node; PET, positron emission tomography; CT, computed tomography; Ip–hilar, ipsilateral hilar; med., mediastinal; SC, subclavicular; cl–hilar, contralateral hilar.

was recorded using the interval-censored techniques. The duration of survival and time to failure were determined from the initiation of the radiation therapy until the date of death and the time of recurrence, respectively. The patients lost to the follow-up were censored at the date of last contact with the institution. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria scale version 2.0.

Statistics

Survival was calculated by the Kaplan–Meier method, and differences in survival were assessed by a log-rank analysis. The factors whose p values were less than 0.10 (borderline significant) in the univariate analysis in Table 1 were further examined using a multivariate analysis. A multivariate analysis for prognostic factors was performed using the Cox

TABLE 2. The Status and the Treatment of Recurrent Diseases in the Patients Who Did Not Receive Radiotherapy

Variables		N = 17
Disease-free interval after surgery, days		482 (97–1297)
Number of stations	Single/multiple	1/16
Site of LN recurrence	N1 level	0
	N2 level	6
	N3 level	11
Symptoms at recurrence	Present/absent	9/8
Maximum diameter of involved LN	20 or smaller/21 or larger	7/10
Treatment for recurrence	Chemotherapy	10
	EGFR-TKI therapy	2
	Supportive care	5
Reason why radiotherapy was not chosen	Extensive lymph node recurrence	6
	Lung fibrosis/COPD	7
	Others	4

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; COPD, chronic obstructive pulmonary disease; LN, lymph node.

proportional hazard regression model. p values less than 0.05 were considered to be statistically significant. The statistical analyses were carried out using the JMP 8 software package (SAS Institute, Cary, NC).

RESULTS

Response to Treatment

Response to treatment was evaluated in all patients but one who died of another cause 4 months after the radiation treatment. Thirty-two of 49 patients (65%) had CR, 12 (24%) had partial response, and five (10%) had progressive disease. A univariate analysis showed that there were no variables associated with the response when patients' response to treatment was divided into with CR and the others. An example of a CR is shown in Figure 2. Relief of the associated symptoms was achieved after radiotherapy in 12 of 13 symptomatic patients. There were 16 patients with elevated CEA values before radiotherapy. Among them, the CEA values responded to radiotherapy in 13 patients (81%), and nine patients (56%) exhibited normal CEA values after radiotherapy.

Progression-Free Survival, Patterns of Failure, and Local Control after Radiotherapy

The median follow-up period after radiation therapy among the survivors was 41 months (range, 19–98 months). Two patients were lost to follow-up at 50 and 73 months after radiotherapy. The remaining survivors received the follow-up per the protocol and the recommendation until this study was closed. Disease progression after radiation therapy was observed in 36 patients (72%). Progression-free survival after radiotherapy is shown in Figure 3*A*. The 1-, 3-, and 5-year progression-free survival rates were 49.1%, 28.2%, and 22.2%, respectively. The median progression-free interval was

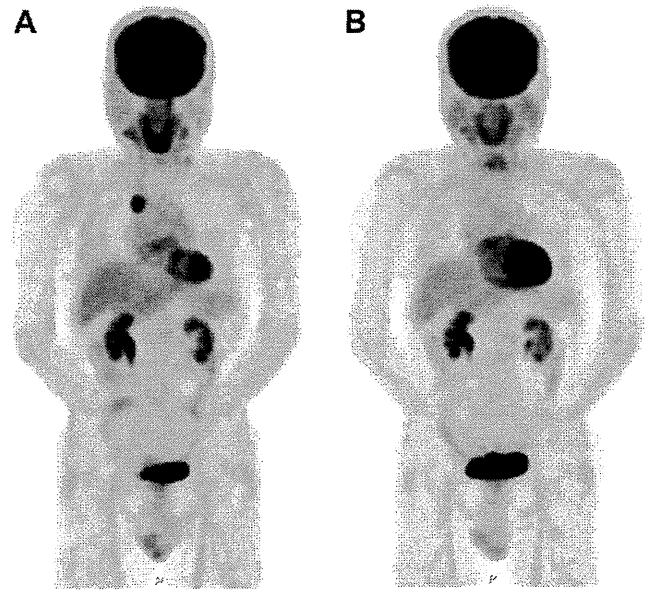

FIGURE 2. An example of complete response to radiotherapy for postoperative lymph node recurrence. PET scans of the whole body were obtained at baseline (*A*) and after 6 months of radiotherapy (*B*). PET, positron emission tomography.

12.0 months after radiotherapy. Ten (23%) of 43 patients who were followed up for more than 3 years showed no additional recurrence after radiotherapy. The initial sites of the disease progression are summarized in Table 3. In-field recurrence was observed in 18 patients (36%) during their entire follow-up period. The probability of local control is shown by the Kaplan–Meier method in Figure 3*B*. The 3- and the 5-year local control rates were 65.9% and 61.1%, respectively. The incidence of initial recurrence in thoracic lymph nodes and the in-field recurrence rate were not associated with the radiotherapeutic approach.

Overall Survival and Prognostic Factors after Radiotherapy

Twenty-seven patients (54%) died of lung cancer and two patients (4%) died of other causes within a 5-year follow-up period. The overall survival probability is shown in Figure 3*C*. The 1-, 3-, and 5-year overall survival rates were 84.0%, 52.7%, and 36.1%, respectively. The median overall survival was 37.3 months after radiotherapy. A univariate analysis was used to evaluate the prognostic impact of 16 clinicopathological factors listed in Table 1. The absence of symptoms and a single involved lymph node station at recurrence were significant favorable prognostic factors but others were not. A multivariate analysis showed that the absence of symptoms and single involved lymph node station were significant independent factors associated with the overall survival (Table 4). The median overall survival was 45.4 months for nonsymptomatic patients and 48.9 months for patients with a single involved lymph node station. There were 23 patients (46%) patients who were both nonsymptomatic and with single involved