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Original Article

Effect of different gross tumor volume longitudinal expansion length on the survival of esophageal squamous cell cancer patients

Hua Zheng[1,2], Yufei Zhou[1,2], Xiyi Liao[1,2], Yimin Li[1,2]

[1]*Department of Radiotherapy, The First Affiliated Hospital of Xiamen University, Xiamen 316003, Fujian, China;* [2]*The Quality Control Center of Radiotherapy in Xiamen City, Xiamen 316003, Fujian, China*

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Abstract: Aims: This study is to compare the therapeutic effects by different longitudinal margin of gross tumor volume (GTV), and to explore the optimization of clinical tumor volume (CTV) in radical chemoradiotherapy of esophageal squamous cell carcinoma (ESCC). Method: ESCC patients treated with chemoradiotherapy for the first time in our hospital from May 2009 to November 2013 were retrospectively analyzed. All the patients were treated by radiotherapy with concurrent chemotherapy and divided into two groups: CTV1 group (GTV longitudinal external expansion length was less than 3 cm) and CTV2 group (GTV longitudinal external expansion length was more than 3 cm). The survival time and incidence of serious side effects of patients was compared. Results: Among the 142 cases of patients, 81 cases belonged to CTV1, and 61 cases belonged to CTV2. There was no significant difference in overall survival (OS) and local failure free survival (LFFS) at year 1, 3, 5 after treatment between the two groups. The incidence of serious side effects more than 3 levels including radiation pneumonitis, radiation esophagitis and esophageal fistula was less than 5% in both groups, and the data in CTV1 was relatively lower. The T stage of American Joint Committee on Cancer (AJCC) before treatment was the independent prognostic factor affecting OS. Conclusion: In radical chemoradiotherapy for ESCC, the OS and the LFFS of patients with a CTV delineated according to a GTV longitudinal external expansion length less than 3 cm is not lower than that of patients with a CTV delineated according to a GTV longitudinal external expansion length more than 3 cm. The incidence of serious side effects more than 3 levels was lower compared with the latter. The results may provide a reference for optimization of CTV in thechemoradiotherapy of ESCC.

Keywords: Esophageal squamous cell carcinoma (ESCC), clinical target volume (CTV), target delineation, survival

Introduction

The incidence of esophageal cancer ranks the 8th in global tumor incidence companied by a mortality which ranks the 6th in the world [1]. In China, more than 95% of esophageal cancer patients are with esophageal squamous cell carcinoma (ESCC) [2]. Radiotherapy is an important method in treatment of esophageal cancer. According to ICRU (International Commission on Radiation Units and Measurements) No 62 document, clinical tumor volume (CTV) includes CTV of esophageal primary lesion (CTV-T) and CTV of lymph drainage area (CTV-N). However, the length of the gross tumor volume of primary tumor (GTV-T) extended along the longitudinal axis of the esophageal primary tumor to constitute the CTV-T is still controversial. CTV-T of esophageal cancer is consisted of main tumor and secondary tumor lesions including direct invasion, intramural metastasis, multi-center origin lesions, vascular invasion, lymph node micrometastases and isolated tumor cells, et al [3]. Research of Tsutsui et al [4] on 400 cases of postoperative pathology samples showed that 95% of esophageal cancer infiltrated directly in a range of no more than 30 mm. But there still have report that the metastasis distance of tumor can be up to 13 cm away from the primary tumor [5]. Gao et al reported that the irradiation field of 94% subclinical lesions of ESCC patients needed to be expanded externally for 30 mm [6]. It still has many different opinions in the expansion from the GTV-T to CTV-T. Clinical studies have shown that radiotherapy in large and complete radiation field including full esophagus and all mediastinal can not

Table 1. Clinical data of patients in CTV1 group and CTV2 group

Clinical data	CTV1 group (n=81)	CTV2 group (n=61)	*P* value
Age (years old)			
Median	62	62	0.419
Range	42-88	43-82	
Gender			
Female	20 (25%)	14 (23%)	0.845
Male	61 (75%)	47 (77%)	
Pathologic type			
Squamous cell	79	58	0.433
Non squamous cell	2	3	
Primary site of tumor			
Neck section	7	5	0.745
Upper thoracic	32	19	
Middle thoracic	34	27	
Lower thoracic	6	7	
Multicenter source	2	3	
T stage			
T1	1	0	0.686
T2	5	2	
T3	30	25	
T4	45	34	
N stage			
N0	44	32	0.826
N+	37	29	
Concurrent chemotherapy			
Yes	32	26	0.708
No	49	35	

improve the local control rate and survival of patients with esophageal cancer, but cause intolerable toxicity to patients instead [7, 8].

It is obviously that the shrink of CTV can reduce irradiation field, and thus reduce the incidence of side effects, such as radiation peneumonitis. However, how long should the GTV-T expand in longitudinal axis is still in debate.

This paper retrospectively analyzed the different therapeutic results in different CTV delineated by external longitudinal expansion of GTV-T in esophageal cancer patients.

Method and materials

Information of patients

A retrospective analysis was performed on 142 patients diagnosed with ESCC and completed radical chemoradiotherapy in our hospital from May 2009 to November 2013. The clinical data of patients was included in **Table 1**. Informed consent was signed by all the patients and certified by Ethics Committee of the First Affiliated Hospital of Xiamen University.

Radiotherapy

According to the longitudinal external expansion length of GTV, the patients were treated with radical chemoradiotherapy and divided into two groups of CTV1 group (Supplementary Figure 1) and CTV2 group (Supplementary Figure 2). In CTV1 group, the longitudinal external expansion length was less than 3 cm. In CTV2 group, the longitudinal external expansion length was more than 3 cm. According to the sixth edition of AJCC Cancer Staging Manual [5] and location of tumor, clinical tumor volume of lymph node was delineated from bilateral supraclavicular, along level 2, level 4, level 5, and level 7, until 3 cm under carina in upper thoracic, from level 2, along level 4, level 5, level 7, and level 8, until the lower boundary of CTV-T in middle thoracic, and from level 4, along level 5, level 7, level 8, cardia side, lesser curvature, until the left gastric lymph node in lower thoracic, respectively. Planning target volume (PTV) was formed by expanding externally for 0.5 cm on the basis of GTVs and CTVs respectively. For GTV-T and GTV of lymphnode, the total dose of 60 Gy/30-33 times (1.8 Gy-2.0 Gy each time) for 5 days every week was used. For CTVs, the total dose of 50 Gy/25-28 times (1.8 Gy-2.0 Gy each time) was used. The 95% PTV were required to be treated with a dose more than 95% prescription dose.

Chemotherapy

Patients of phase II or above received concurrent chemotherapy from the first day of radiotherapy. Program 1 was preferred in chemotherapy, and program 2 was selected if there was paclitaxel allergy. Patients aged over 70 years did not receive the concurrent chemotherapy. Program 1: Cisplatin was used with a dose of 25 mg/m^2 and cisplatin treatment lasted for 3 days. Paclitaxel was used with a dose of 135 mg/m^2 on the first day of chemotherapy. Two treatment courses were performed, with

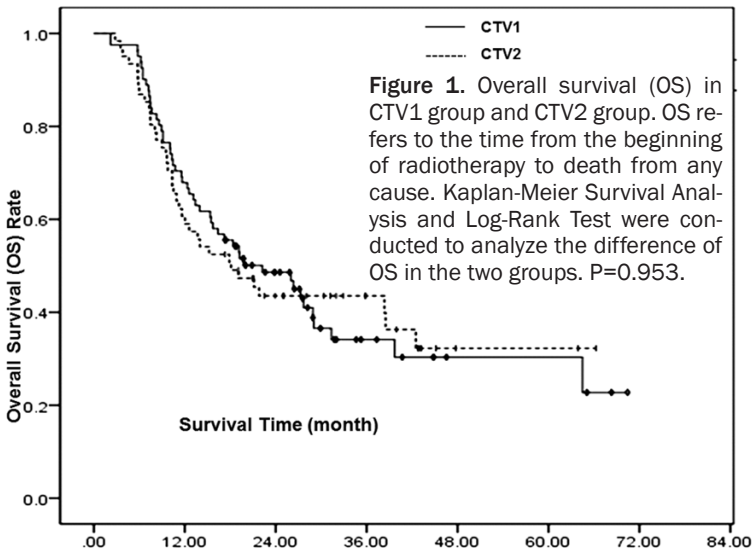

Figure 1. Overall survival (OS) in CTV1 group and CTV2 group. OS refers to the time from the beginning of radiotherapy to death from any cause. Kaplan-Meier Survival Analysis and Log-Rank Test were conducted to analyze the difference of OS in the two groups. P=0.953.

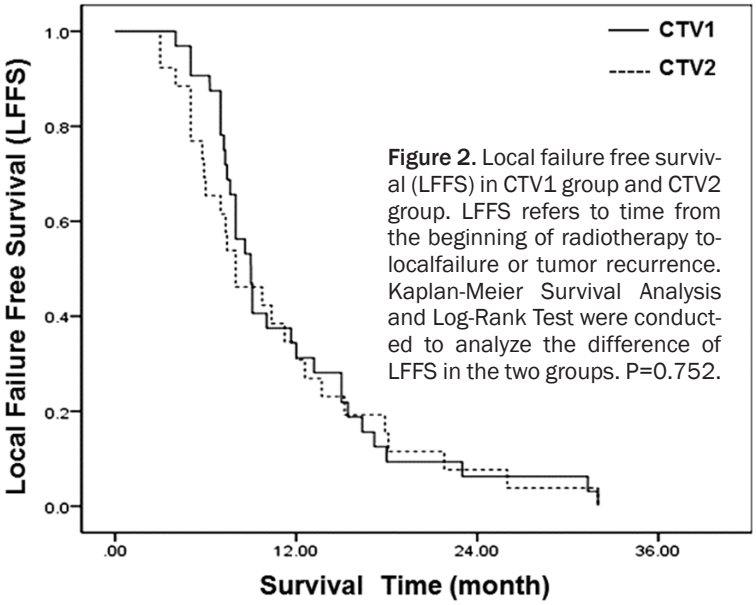

Figure 2. Local failure free survival (LFFS) in CTV1 group and CTV2 group. LFFS refers to time from the beginning of radiotherapy to localfailure or tumor recurrence. Kaplan-Meier Survival Analysis and Log-Rank Test were conducted to analyze the difference of LFFS in the two groups. P=0.752.

the interval time of 28 days. Program 2: Cisplatin was used with a dose of 25 mg/m^2 and cisplatin treatment lasted for 3 days. Then a 5-day-continuous use of 5-fluorouracil (5-FU) in a dose of 500 mg/m^2 was performed. Two treatment courses were performed, with the interval time of 28 days.

Following-up of patients

The following-up started from the beginning of radiotherapy till to the deadline. Data of patients died of esophageal cancer were classified as complete data, and censored data included data of patients surviving with or without tumor and data of patients died of complications of radiotherapy or other diseases. Survival time was time from the beginning of radiotherapy until death or the end of following-up. Reexamination was performed once each 3 months in 2 years and 6 months from 3 to 5 years after treatment. Examination included CT scanning on chest, esophageal barium meal, esophagoscopy and abdominal ultrasound, and body bone scanning in patients with bone pain. Until the deadline of the following-up on April 1st 2015, all the 142 cases were followed up completely with a median time of 31 months (2 months to 55 months).

Statistical analysis

All the measurement data were presented as mean ± standard deviation (SD). Statistical analysis was performed using SPSS 19.0 soft package. χ^2 test was used to compare the difference of the characteristics of the two groups. Log-Rank test was conducted to analyze survival difference. Kaplan-Meier and Cox's Proportionally Hazards Regression Model were performed to analysis the risk factors affecting survival time. Regression analysis was used to compare the rate of complications. $P < 0.05$ was considered significantly different.

Results

Survival analysis

To determine the difference in therapy efficacy and prognosis between the two groups, all the cases were followed up after treatment, and the survival and local recurrence of patients were analyzed statistically. Overall survival (OS)

Table 2. The incidence of side effects of radiotherapy

Side effects (≥3 grade)	CTV1 group (n=81)	CTV2 group (n=61)
Pulmonary	0	1
Esophageal	2	2

Note: Side effects were clarified according to the acute radiation injury criteria of Radiation Therapy Oncology Group (RTOG). There was no significant difference between the two groups detected using regression analysis. P=0.437.

Table 3. Differences of effects of part clinical data on OS

	χ^2 value	*P* value
Gender	0.651	0.420
Age	0.064	0.800
Primary site	4.26	0.372
Pathological differentiation	0.265	0.876
AJCC T stage	14.7	0.002
CTV classification	0.003	0.953

Note: The age of 65 years old was considered to be the boundary of age. Differences were detected by Log-Rank Test.

time for each patient was shown in Supplementary Table 1. Till the end of following-up, 50 cases of the total 81 cases died of tumor or tumor relevant complications in CTV1 group, and the OS at 1, 3, and 5 years after treatment of this group was 67.9%, 34.1% and 30.3%, respectively. And, 37 cases of the total 61 cases died of tumor or tumor relevant complications in CTV2 group, and the OS at 1, 3, and 5 years after treatment of this group was 61%, 43% and 32%, respectively (**Figure 1**). The local failure free survival (LFFS) for each patient was shown in Supplementary Table 2. It was found that the local failure free survival (LFFS) at 1, 3, and 5 years after treatment was 87.4%, 24.4% and 8.1% in CTV1 group and 88.8%, 27.6% and 7.9% in CTV2 group, respectively (**Figure 2**). Log-Rank Test showed no significant difference between data of the two groups. The results indicated that there was no significant difference in therapy efficacy and prognosis between the two groups.

Side effects

According to the acute radiation injury classification criteria from Therapy Oncology Group (RTOG), the incidence of late side effects more than 3 levels which were related with esophagus and lung were lower than 5% in both group. There was only one case of esophageal fistula in each group. Regression analysis results showed no significant difference between the two groups (**Table 2**).

Clinical factors, efficacy and prognosis

To clarify if the efficacy and prognosis of the two groups were related with clinical factors, Cox regression were conducted to analyze the effects of gender, age, primary tumor site, pathological type and AJCCT stage on OS. It was found that there was no significant difference between clinical factors mentioned above except AJCCT stage (**Table 3**).

Discussion

In this paper, different CTV delineated by an longitude external expansion distance of 3 cm or more than 3 cm of GTV, to clarify the different therapeutic effects of chemoradiotherapy on ESCC. The OS, incidence of severe side effects and LFFS between the two groups were compared. The optimization of CTV in radical chemoradiotherapy of ESCC was discussed.

Clinical studies have shown that radiotherapy combined with concurrent chemotherapy can improve the survival in esophageal cancer [7, 8]. However, the large and complete radiation field causes intolerable toxicity to patients and the range of GTV external expansion in treatment has not been clarified yet [8, 17-19]. In our study, results showed that there was no significant difference in OS and LFFS of patients treated on different CTV, which was delineated by the external expansion distance along the longitudinal axis of GTV (≤ 3 cm or ≥ 3 cm) in radical chemoradiotherapy of ESCC. This indicates that in radiotherapy for esophageal cancer, an external expansion distance less than 3 cm of GTV along esophageal longitudinal axis is conductive to further refine CTV of esophageal cancer and may reduce side effects of radiotherapy. Our results were consistent with results of published papers. For example, Button [21] collected 145 patients with esophageal cancer received radical chemoradiotherapy. All the patients were treated on the same external expansion boundary of subclinical lesions, which was a 2 cm external expansion up and down the primary tumor GTV defined by

endoscopic ultrasonography and (or) CT and a 1 cm external expansion surrounding esophageal tube. The results showed that the failure rate occurred in irradiation field was only 4%. However, most of the subjects in Button's research are patients with adenocarcinoma, which has a different biologic character to ours.

Since the incidence of severe side effects after radiotherapy of esophageal cancer, such as radiation pneumonitis, is not low [16], it is possible to reduce the incidence of these complications if the therapy target area can be further refined. Our results also showed that the incidence of severe side effects was lower in patients with the CTV-T formed by a 3 cm external expansion of GTV along the longitude axis, compared with that in patients with the CTV formed by a more than 3 cm external expansion of GTV along the longitude axis under the same therapeutic conditions. In addition, due to the advances in imaging technology, it is possible to find a smaller lymph node metastasis and improve the efficacy of radiation therapy. For example, new imaging technologies like PET/CT are more sensitive to find out lymph node metastasis of esophageal cancer earlier than CT. Okada M et al [22] conducted a retrospective analysis on 210 patients diagnosed with esophageal cancer pathologically. The analyzed data included preoperative standardized uptake value (SUV) of PET/CT and image data of venous enhanced CT of lymph node before surgeryon lymph nodes. It was found that the positive predictive value on lymph nodes of PET/CT was higher than that of venous enhanced CT. Kato et al [23] analyzed the preoperative images of 167 patients with thoracic ESCC treated with surgery. The results showed that PET/CT was more sensitive in diagnosis of neck, upper mediastinum, and abdominal lymph nodes compared to PET. Therefore, we speculate that it may be a further research direction to define the metastatic lymph nodelesion of esophageal cancer using PET/CT images. In addition, due to the continuous advent of chemotherapy drugs, it is possible to rely on chemotherapy to kill the tiny metastatic lesions, which can not be detected by the new imaging technology such as PET/CT. Hence the radiation therapy target can be refined.

In conclusion, the OS and LFFS of patients treated on CTV formed by a 3 cm external expansion of GTV in this study was not lower than that in patients with a more than 3 cm external expansion of GTV on the same therapeutic condition, and the incidence of severe side effects of radiotherapy in the former group was lower. The results suggest that it is feasible to define GTV with a 3 cm external expansion as CTV-T treated in radical chemoradiotherapy of ESCC. And, it is conducive to further refine the CTV of ESCC and thus may reduce the incidence of severe side effects of radiotherapy.

Disclosure of conflict of interest

None.

Address correspondence to: Yimin Li, Department of Radiotherapy, The First Affiliated Hospital of Xiamen University; The Quality Control Center of Radiotherapy in Xiamen City, No. 55, Zhen Hai Road, Xiamen 316003, Fujian, China. Tel: +86 592-2139175; 2139532; E-mail: xmliyimin@126.com

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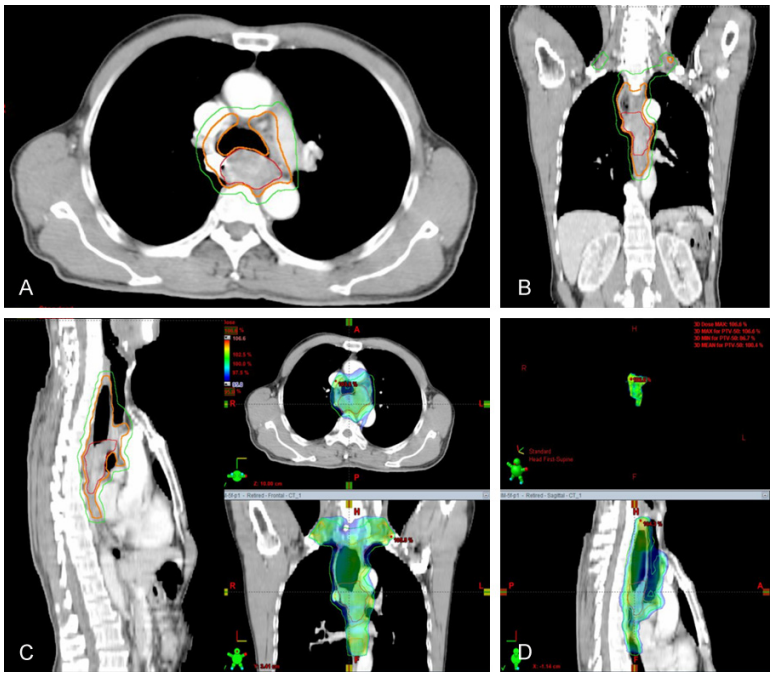
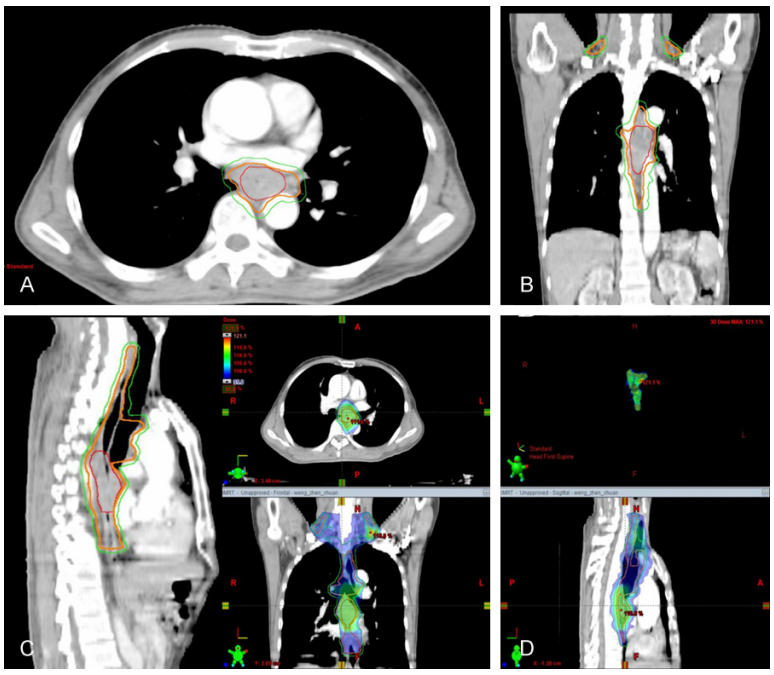


Supplementary Figure 1. Images of one patient selected randomly from group CTV1. A-D was the horizontal, coronal, sagittalplane of the target and the dose distribution of the radiationplan. The red, orange and green lines were used to contour GTV, CTV, and PTV, respectively.



Supplementary Figure 2. Images of one patient selected randomly from group CTV2. A-D was the horizontal, coronal, sagittalplane of the target and the dose distribution of the radiationplan. The red, orange and green line were used to contour GTV, CTV, and PTV, respectively.

Supplementary Table 1. Overall survival time for each patient

Patient no.	Gross tumor volume longitudinal expansion length (cm)	Death	Overall survival time (month)
2	≤ 3 cm	No	68.30
4	≤ 3 cm	No	70.43
6	> 3 cm	No	66.26
10	≤ 3 cm	No	65.05
15	> 3 cm	No	63.90
24	> 3 cm	No	45.14
29	≤ 3 cm	No	44.84
32	≤ 3 cm	No	44.78
39	> 3 cm	No	43.23
45	> 3 cm	No	43.07
48	> 3 cm	No	42.77
59	≤ 3 cm	No	40.70
60	≤ 3 cm	No	46.52
62	> 3 cm	No	39.95
76	≤ 3 cm	No	37.32
77	> 3 cm	No	35.87
78	> 3 cm	No	35.81
80	≤ 3 cm	No	35.25
85	> 3 cm	No	32.88
89	> 3 cm	No	31.96
92	≤ 3 cm	No	31.96
95	> 3 cm	No	30.35
102	≤ 3 cm	No	29.89
108	> 3 cm	No	31.21
109	≤ 3 cm	No	31.73
112	≤ 3 cm	No	34.62
118	≤ 3 cm	No	28.18
121	> 3 cm	No	28.05
124	≤ 3 cm	No	28.91
126	≤ 3 cm	No	27.53
127	≤ 3 cm	No	27.13
129	≤ 3 cm	No	26.44
139	> 3 cm	No	25.06
140	> 3 cm	No	24.96
146	≤ 3 cm	No	24.54
148	≤ 3 cm	No	23.85
149	> 3 cm	No	23.91
151	≤ 3 cm	No	23.81
162	> 3 cm	No	22.53
169	> 3 cm	No	21.09
172	≤ 3 cm	No	20.86
178	≤ 3 cm	No	20.00
179	> 3 cm	No	20.92
185	> 3 cm	No	19.08
186	≤ 3 cm	No	19.71

190	≤ 3 cm	No	18.62
193	≤ 3 cm	No	19.71
195	> 3 cm	No	17.31
196	≤ 3 cm	No	17.31
3	> 3 cm	Yes	14.00
5	≤ 3 cm	Yes	22.21
7	≤ 3 cm	Yes	29.01
9	≤ 3 cm	Yes	27.66
11	≤ 3 cm	Yes	26.02
13	≤ 3 cm	Yes	39.69
14	≤ 3 cm	Yes	13.40
21	> 3 cm	Yes	12.02
43	≤ 3 cm	Yes	10.78
44	≤ 3 cm	Yes	6.21
51	> 3 cm	Yes	42.50
53	> 3 cm	Yes	10.51
63	> 3 cm	Yes	10.91
66	> 3 cm	Yes	6.70
81	≤ 3 cm	Yes	13.96
84	≤ 3 cm	Yes	10.32
94	> 3 cm	Yes	7.46
111	≤ 3 cm	Yes	8.90
113	≤ 3 cm	Yes	6.47
115	≤ 3 cm	Yes	18.37
119	≤ 3 cm	Yes	26.32
122	≤ 3 cm	Yes	7.49
164	> 3 cm	Yes	21.13
167	≤ 3 cm	Yes	12.55
171	≤ 3 cm	Yes	12.35
173	≤ 3 cm	Yes	8.25
18	> 3 cm	No	47.77
46	> 3 cm	No	42.77
135	≤ 3 cm	No	25.82
161	≤ 3 cm	No	22.60
189	≤ 3 cm	No	18.79
198	≤ 3 cm	No	17.41
8	≤ 3 cm	Yes	10.41
12	> 3 cm	Yes	9.53
17	≤ 3 cm	Yes	19.12
20	≤ 3 cm	Yes	6.90
22	> 3 cm	Yes	5.82
23	> 3 cm	Yes	19.09
25	> 3 cm	Yes	9.63
26	> 3 cm	Yes	8.05
27	≤ 3 cm	Yes	5.82
28	> 3 cm	Yes	15.21
30	> 3 cm	Yes	38.51
31	≤ 3 cm	Yes	17.18
33	> 3 cm	Yes	2.79

34	≤ 3 cm	Yes	2.20
34	≤ 3 cm	Yes	64.46
35	≤ 3 cm	Yes	11.56
38	≤ 3 cm	Yes	10.12
40	> 3 cm	Yes	10.35
41	> 3 cm	Yes	3.52
42	> 3 cm	Yes	11.63
54	> 3 cm	Yes	4.63
55	> 3 cm	Yes	11.24
56	> 3 cm	Yes	8.97
57	> 3 cm	Yes	8.25
58	≤ 3 cm	Yes	31.34
61	≤ 3 cm	Yes	15.38
70	≤ 3 cm	Yes	5.78
72	≤ 3 cm	Yes	13.17
73	> 3 cm	Yes	38.34
79	≤ 3 cm	Yes	19.75
82	≤ 3 cm	Yes	15.44
83	≤ 3 cm	Yes	7.23
86	> 3 cm	Yes	10.35
87	> 3 cm	Yes	9.76
91	≤ 3 cm	Yes	6.47
93	≤ 3 cm	Yes	15.70
96	> 3 cm	Yes	5.98
97	> 3 cm	Yes	21.82
98	> 3 cm	Yes	17.87
99	≤ 3 cm	Yes	10.05
100	> 3 cm	Yes	7.33
101	≤ 3 cm	Yes	7.29
103	≤ 3 cm	Yes	8.61
106	> 3 cm	Yes	3.81
114	≤ 3 cm	Yes	28.91
116	≤ 3 cm	Yes	6.28
120	> 3 cm	Yes	5.78
125	≤ 3 cm	Yes	27.30
128	≤ 3 cm	Yes	2.20
130	≤ 3 cm	Yes	9.10
132	≤ 3 cm	Yes	7.62
136	> 3 cm	Yes	7.43
147	≤ 3 cm	Yes	16.39
150	≤ 3 cm	Yes	7.43
155	> 3 cm	Yes	18.10
156	> 3 cm	Yes	5.88
166	> 3 cm	Yes	12.58
168	> 3 cm	Yes	13.70
174	≤ 3 cm	Yes	9.10
183	≤ 3 cm	Yes	19.25
194	≤ 3 cm	Yes	11.66

Supplementary Table 2. The local failure free survival (LFFS) for each patient

Patient no.	Gross tumor volume longitudinal expansion length (cm)	Local failure	Local failure free survival (month)
2	≤ 3 cm	No	68.30
4	≤ 3 cm	No	70.43
6	> 3 cm	No	66.26
10	≤ 3 cm	No	65.05
15	> 3 cm	No	63.90
24	> 3 cm	No	45.14
29	≤ 3 cm	No	44.84
32	≤ 3 cm	No	44.78
39	> 3 cm	No	43.23
45	> 3 cm	No	43.07
48	> 3 cm	No	42.77
59	≤ 3 cm	No	40.70
60	≤ 3 cm	No	46.52
62	> 3 cm	No	39.95
76	≤ 3 cm	No	37.32
77	> 3 cm	No	35.87
78	> 3 cm	No	35.81
80	≤ 3 cm	No	35.25
85	> 3 cm	No	32.88
89	> 3 cm	No	31.96
92	≤ 3 cm	No	31.96
95	> 3 cm	No	30.35
102	≤ 3 cm	No	29.89
108	> 3 cm	No	31.21
109	≤ 3 cm	No	31.73
112	≤ 3 cm	No	34.62
118	≤ 3 cm	No	28.18
121	> 3 cm	No	28.05
124	≤ 3 cm	No	28.91
126	≤ 3 cm	No	27.53
127	≤ 3 cm	No	27.13
129	≤ 3 cm	No	26.44
139	> 3 cm	No	25.06
140	> 3 cm	No	24.96
146	≤ 3 cm	No	24.54
148	≤ 3 cm	No	23.85
149	> 3 cm	No	23.91
151	≤ 3 cm	No	23.81
162	> 3 cm	No	22.53
169	> 3 cm	No	21.09
172	≤ 3 cm	No	20.83
178	≤ 3 cm	No	20.00
179	> 3 cm	No	20.92
185	> 3 cm	No	19.08
186	≤ 3 cm	No	19.71

190	≤ 3 cm	No	18.62
193	≤ 3 cm	No	19.71
195	> 3 cm	No	17.31
196	≤ 3 cm	No	17.31
3	> 3 cm	No	14.00
5	≤ 3 cm	No	18.00
7	≤ 3 cm	No	25.00
9	≤ 3 cm	No	15.00
11	≤ 3 cm	No	22.00
13	≤ 3 cm	No	39.69
14	≤ 3 cm	No	13.40
21	> 3 cm	No	6.00
43	≤ 3 cm	No	10.78
44	≤ 3 cm	No	6.21
51	> 3 cm	No	17.00
53	> 3 cm	No	7.00
63	> 3 cm	No	10.91
66	> 3 cm	No	6.70
81	≤ 3 cm	No	13.96
84	≤ 3 cm	No	10.32
94	> 3 cm	No	7.46
111	≤ 3 cm	No	8.90
113	≤ 3 cm	No	6.47
115	≤ 3 cm	No	9.00
119	≤ 3 cm	No	19.00
122	≤ 3 cm	No	7.49
164	> 3 cm	No	21.13
167	≤ 3 cm	No	12.55
171	≤ 3 cm	No	12.35
173	≤ 3 cm	No	8.25
18	> 3 cm	Yes	32.00
46	> 3 cm	Yes	12.00
135	≤ 3 cm	Yes	23.00
161	≤ 3 cm	Yes	9.00
189	≤ 3 cm	Yes	18.00
198	≤ 3 cm	Yes	9.00
8	≤ 3 cm	Yes	7.00
12	> 3 cm	Yes	3.00
17	≤ 3 cm	Yes	7.00
20	≤ 3 cm	Yes	5.00
22	> 3 cm	Yes	4.00
23	> 3 cm	Yes	5.00
25	> 3 cm	Yes	6.00
26	> 3 cm	Yes	3.00
27	≤ 3 cm	Yes	4.00
28	> 3 cm	Yes	15.21
30	> 3 cm	Yes	7.00
31	≤ 3 cm	Yes	17.18
33	> 3 cm	Yes	2.79

34	≤ 3 cm	Yes	2.20
34	≤ 3 cm	Yes	32.00
35	≤ 3 cm	Yes	8.00
38	≤ 3 cm	Yes	7.00
40	> 3 cm	Yes	8.00
41	> 3 cm	Yes	3.52
42	> 3 cm	Yes	8.00
54	> 3 cm	Yes	4.63
55	> 3 cm	Yes	11.24
56	> 3 cm	Yes	5.00
57	> 3 cm	Yes	5.00
58	≤ 3 cm	Yes	31.34
61	≤ 3 cm	Yes	12.00
70	≤ 3 cm	Yes	5.78
72	≤ 3 cm	Yes	13.17
73	> 3 cm	Yes	26.00
79	≤ 3 cm	Yes	15.00
82	≤ 3 cm	Yes	15.44
83	≤ 3 cm	Yes	7.23
86	> 3 cm	Yes	10.35
87	> 3 cm	Yes	9.76
91	≤ 3 cm	Yes	4.00
93	≤ 3 cm	Yes	5.00
96	> 3 cm	Yes	5.98
97	> 3 cm	Yes	21.82
98	> 3 cm	Yes	17.87
99	≤ 3 cm	Yes	10.05
100	> 3 cm	Yes	7.33
101	≤ 3 cm	Yes	7.29
103	≤ 3 cm	Yes	8.61
106	> 3 cm	Yes	3.81
114	≤ 3 cm	Yes	8.00
116	≤ 3 cm	Yes	6.28
120	> 3 cm	Yes	5.78
125	≤ 3 cm	Yes	15.00
128	≤ 3 cm	Yes	2.20
130	≤ 3 cm	Yes	9.10
132	≤ 3 cm	Yes	7.62
136	> 3 cm	Yes	7.43
147	≤ 3 cm	Yes	16.39
150	≤ 3 cm	Yes	7.43
155	> 3 cm	Yes	18.10
156	> 3 cm	Yes	5.88
166	> 3 cm	Yes	12.58
168	> 3 cm	Yes	13.70
174	≤ 3 cm	Yes	9.10
183	≤ 3 cm	Yes	8.00
194	≤ 3 cm	Yes	11.66