International Journal of Gerontology 18 (2024) 42–47
https://doi.org/10.6890/IJGE.202401_18(1).0008

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Efficacy of Definitive Radiotherapy for Stage II–III Cervical Cancer in Elderly Patients

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ARTICLE INFO

Accepted 8 June 2023

Keywords:
aged,
uterine cervical neoplasms,
radiotherapy,
prognosis

SUMMARY

Background: Elderly patients treated with radiotherapy (RT) for advanced cervical cancer are more likely to suffer severe treatment-related toxicity due to underlying comorbidities. Severe toxicity may lead to treatment interruptions, reduced overall survival (OS), worse comorbidities, and poor quality of life. Therefore, there is a need to optimize the treatment of these patients to improve clinical outcomes. This study aimed to identify the prognostic factors for survival and treatment-related toxicities in elderly cervical cancer patients treated with definitive RT.

Methods: From January 2005 to June 2012, 103 patients aged 75 years and older diagnosed with cervical cancer were enrolled in our study. The median age was 77 years. All patients were treated with both external beam radiotherapy (EBRT) and high dose rate intracavitary brachytherapy (HDR-ICBT). The OS rate was analyzed using the Kaplan-Meier method. Acute and chronic toxicity was evaluated during follow-up appointments using the Common Terminology Criteria for Adverse Events version 3.0. Univariate and multivariate analyses were used to identify the impact of patient comorbidities, tumor stage, and RT treatment on toxicity and survival.

Results: The patient follow-up rate was 92.23%. The one, three, and five-year OS rates were 96.1%, 67.2%, and 60.2%, respectively. None of the patients developed grade III or IV GI/GU toxicity during RT. Ten patients developed grade 2 or higher radiation proctitis. The univariate analysis showed that pelvic lymph node involvement with or without para-aortic lymph node metastasis (PLN ± PALN), primary tumor size, and radiation dose were the three main factors influencing OS, while the Chalson comorbidity disease score had no impact on OS. Following multivariate analysis, PLN ± PALN, primary tumor size, and radiation dose were identified as independent factors affecting long-term survival.

Conclusions: Definitive RT is well tolerated in elderly patients with multiple comorbidities.

1. Background

In 2015, the average life expectancy in China was 76.34 years and is expected to reach an average of 79.0 years by 2030.[1] Advances in healthcare treatment and an aging population will eventually result in a higher incidence of cervical cancer in elderly women. Radical hysterectomy is often considered the treatment of choice for early-stage cervical cancer when feasible. Although some studies have shown that surgery is a feasible treatment option for elderly patients diagnosed with early-stage disease,[2,3] it is rarely offered to these patients, and pelvic lymphadenectomy is rarely performed in elderly patients.[6,8] Elderly patients are more likely to have underlying comorbidities and are often not fit for surgery.[4,5] Furthermore, George et al.[7] reported that the perioperative mortality rate for women above 70 years of age was 30 times higher than that of women below the age of 50.

Radiotherapy (RT) provides a non-invasive alternative treatment to surgery. Previous studies have shown that RT is a more appropriate treatment for the elderly patient population,[7,9–11,16–22] particularly for those patients who are medically inoperable due to underlying comorbidities, have advanced disease, or refuse to have surgery. The National Comprehensive Cancer Network guidelines state that RT can be used to treat early-stage diseases, and its importance increases for more advanced diseases.[24]

Elderly patients treated with RT for advanced cervical cancer are more likely to suffer severe treatment-related toxicity due to underlying comorbidities.[10] Severe toxicity may lead to treatment interruptions, poor compliance with the treatment, and worse comorbidities. This will eventually compromise the efficacy of the treatment and lead to poor quality of life, highlighting the need to optimize the treatment for these patients based on prognostic factors. Therefore, the study aimed to retrospectively identify prognostic factors for the development of treatment-related toxicity and overall survival (OS) in elderly cervical cancer patients.

2. Methods

From January 2005 to June 2012, 103 patients aged 75 years and above with stage II or III cervical cancer were enrolled in the study. All patients were treated by standard definitive RT techniques at a Chinese hospital. The treatment consisted of external beam radiotherapy (EBRT) followed by high dose rate intracavitary brachytherapy (HDR-ICBT). Patients were included in the study if they had a

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pathologically confirmed diagnosis of cervical cancer with no evidence of distant organ metastasis or mediastinal, inguinal, and supraclavicular lymph node metastasis and completed at least two-thirds of a prescribed RT course using at least 60 Gy. Patients who had previous surgery or RT to the pelvis or contraindications for radiotherapy were excluded from the study.

The patients' demographics, tumor stage, RT prescription, underlying comorbidities, and the Charlson comorbidity index (CCI)[32] were recorded for each patient, as shown in Table 1.

2.1. Radiotherapy

2.1.1. EBRT

The EBRT was delivered to the whole pelvis using either 6 MV or 10 MV photons on a linear accelerator. The patients were planned using 3D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). EBRT consisted of either 40 Gy to 46 Gy in 20–23 fractions to the whole pelvis or 45 to 50.4 Gy in 25 to 28 fractions. Patients with positive common iliac or para-aortic lymph nodes (PALNS) received extended-field EBRT, including the PALNS. An additional boost of 7.2 Gy to 10.8 Gy in 4 to 6 fractions was provided to the parametrium or involved lymph nodes in between the HDR-ICBT fractions using EBRT. The median total EBRT dose was 50.4 Gy (40.0 Gy to 61.2 Gy).

2.1.2. HDR-ICBT

The HDR-ICBT was done with a Microselectron HDR (Nucletron, The Netherlands) using a 192-Iridium remote afterloading system. The treatment was provided during or after the EBRT. The median total dose to point A was 28.0 (range from 14.0–35.0 Gy) with a dose per fraction of 6.0 to 7.0 Gy once or twice a week. If the lower two-thirds of the vagina was involved, the dose at the vaginal reference point (5 mm below the mucosa) was 12 to 28 Gy. Treatment planning for HDR-ICBT was performed at each irradiation using the PLATO Brachytherapy Planning System version 3.2 (Nucletron, The Netherlands). Rectal and bladder doses were assessed according to the International Commission on Radiation Units and Measurements Report 38.[34] The median dose at the rectal and bladder points was 18.2 Gy (range from 16.8 to 24.5 Gy) and 21 Gy (range from 19.6 Gy to 28 Gy), respectively.

2.2. Observation and follow-up

All adverse reactions and the corresponding clinical symptoms during the treatment were recorded. Routine follow-up visits were performed by three gynecologic radiation oncologists every three months for the first two years, every six months for the next three years, and yearly thereafter. During the follow-up visits, a physical examination, Papanicolau smear, routine blood test, and serum tumor markers were analyzed. Additional radiographic examinations were performed if disease recurrence was suspected. The patient's survival status, with or without recurrence, metastasis, and recurrence or metastatic sites were also recorded. Acute and chronic toxicity were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0.[33]

2.3. Statistical analysis

All analyses were performed using the statistical product and service solutions (SPSS) software. Univariate analysis using the Kaplan-Meier method was used to analyze the patient's OS. The Cox proportional hazard model was used for the multivariate analysis.

3. Results

3.1. Patient and tumor characteristics

The patients' and tumor characteristics are summarized in Table 1. A total of 103 patients were included in the study, of whom 99 had squamous cell carcinoma, and four had an adenocarcinoma. Of the 4 adenocarcinomas, 1 was classified as mucinous adenocarcinoma, and the rest were typical adenocarcinomas. A total of fifty-three pa-

Table 1
Patients, tumor, and treatment characteristics.

	Characteristic	No. of patients	Percentage (%)
Age (years old)	Median	77	
75–79		74	71.84
≥ 80		29	28.16
Karnofsky score	90	97	94.17
	80	5	4.85
	70	1	0.97
Charlson comorbidity score	0	50	48.54
	1	35	33.98
	2	18	17.48
Histology	Squamous cell carcinoma	99	96.12
	Adenocarcinoma	4	3.88
Stage	IIa	18	17.48
	IIb	36	34.95
	IIIa	11	10.68
	IIIb	38	36.89
Lymph node metastasis	Pelvic	13	12.62
	Para-aortic	2	1.94
	Pelvic and para-aortic	2	1.94
EBRT technique	3D–CRT	91	88.35
	IMRT	12	11.65
Completion of radiotherapy	Whole course	74	71.84
	Incomplete course	29	28.16
Duration of radiotherapy	> 8 weeks	3	2.91
	≤ 8 weeks	100	97.09

EBRT: external beam radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy.

tients presented with comorbidities such as cardiovascular disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and anemia. Thirty-five patients presented with one concurrent condition, 13 patients had two comorbidities, and five had three or more comorbidities. Ninety-one patients were treated with 3D-CRT, and the remaining 12 received IMRT. None of the patients in this study received chemotherapy.

Seventy-four patients completed the entire RT treatment and received a total dose of 85 Gy or higher and a biologically effective dose (BED) of 10 Gy. Twenty-nine patients could not complete the entire radiotherapy procedure and received a lower dose ranging from 60 to 75 Gy. Of these 29 patients, 15 did not complete the treatment due to treatment-related toxicity, and 14 did not comply with the treatment. All patients completed the RT treatment within eight weeks, with the only exception of three cases. One of these patients experienced diarrhea, and the other two cases experienced a respiratory tract infection during treatment.

3.2. Patient follow-up

Patient follow-up began when all treatment was finished. Up until June 2017, eight cases had been lost through follow-up, resulting in a final overall follow-up rate of 92.23%.

3.3. Toxicity

The acute and late toxicities experienced by the patients are summarised in Table 2. During treatment, five patients experienced urinary frequency and dysuria, and 23 patients developed gastrointestinal (GI) toxicity. None of the patients experienced grade III or IV gastrointestinal or urinary toxicity. Twenty-four patients experienced grade I or II myelosuppression, and two patients experienced grade III myelosuppression. Twenty-nine patients experienced grade I or II vaginal mucositis, and twenty patients experienced grade I or II perineal dermatitis. All symptoms disappeared after treatment.

Overall the incidence of late toxicity was low. Only four patients developed hematuria at 11, 14, 15, and 17 months after treatment. Cystoscopy showed bladder mucosal congestion changes in these patients. After receiving treatment, two patients totally recovered from hematuria, while the other two patients showed improvement. Twelve patients developed grade I radiation proctitis and were cured after symptomatic treatment. Eight patients experienced grade II radiation proctitis. After receiving an enema and anti-inflammatory treatment, seven patients improved significantly, while only one patient continued to experience repeated rectal bleeding. One patient developed grade III radiation proctitis. One patient developed a rectovaginal fistula with local tumor progression, and another patient developed long-term diarrhea. Six patients developed vaginal stenosis.

A total of 15 patients did not complete the treatment as they developed either grade II perineal dermatitis (n = 8), grade II–III hematologic toxicity (n = 3), worsening of gastrointestinal or hematologic toxicity (n = 3), and renal insufficiency due to urethral obstruction (n = 1).

Table 2
Acute and chronic toxicity.

	I (case)	II (case)	III (case)	IV (case)
Acute toxicity				
Hematologic toxicity	11	13	2	
GI toxicity	21	2		
Urinary toxicity	5			
Vaginal mucositis	24	5		
Perineal dermatitis	5	15		
Chronic toxicity				
Radiation proctitis	12	8	1	1
GI toxicity	2			
Urinary toxicity	2	2		
Vaginal stenosis	3	2	1	

GI: gastrointestine.

3.4. Overall survival

The one, three, and five-year OS rates were 96.1%, 67.2%, and 60.2%, respectively. Thirty-eight patients survived for more than five years without tumor recurrence. Two of these patients, who were 78 and 79 years old at the time of initial treatment, survived more than10 and 12 years, respectively.

One patient with mucinous adenocarcinoma died of systemic metastases after 35 months following treatment, and 2 patients diagnosed with typical adenocarcinoma died of local persistent and mediastinal metastasis at 13 and 31 months after treatment, respectively. One patient was alive for 56 months, free of disease at the time of the last follow-up.

3.5. Cause of death

Tumor progress (n = 14) was the common cause of death, followed by tumor progression (n = 9), tumor recurrence (n = 9), distance metastasis (n = 8), and recurrence with distance metastasis (n = 3). Two patients died due to radiation-induced proctitis, and another two patients died from tumor recurrence with radiation proctitis (n = 2). All other patients died due to either underlying comorbidities (n = 4), natural causes (n = 7), or other causes (n = 6) unrelated to this study.

3.6. Factors affecting survival

Univariate survival analysis revealed that the five-year OS of patients with a primary tumor size below 5 cm and greater than 5 cm was 72% and 42%, respectively (p = 0.001, Figure 1). The five-year OS of patients without lymph node metastasis and with pelvic and/or para-aortic lymph node involvements (PLN ± PALN) was 66.20% and 27.50%, respectively (p = 0.001, Figure 2). The five-year OS of patients receiving a total radiation dose above or equal to 85 Gy and below 75 Gy was 67.20% and 43.00%, respectively (p = 0.002, Figure 3). The stage, range of vaginal involvement, and CCI had no impact on OS (see Table 3).

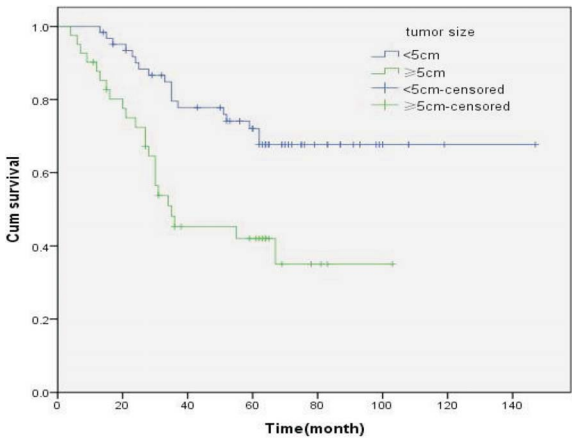

Figure 1. Primary tumor size and efficacy.

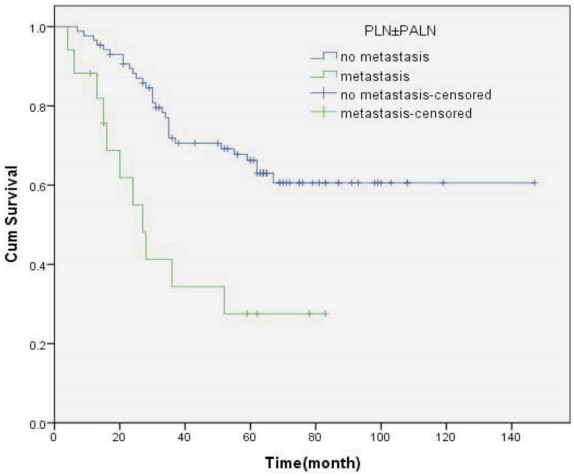

Figure 2. PLN ± PALN and efficacy.

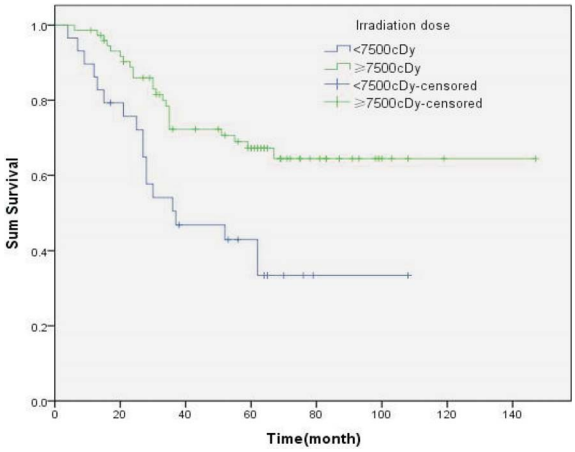

Figure 3. Irradiation dose and efficacy.

Table 3
Univariate analysis of patients.

Clinical factors	Cases	5-yr OS (%)	p
Charlson comorbidity score			0.83
0	50	60.50	
1	35	61.20	
2	18	51.86	
Stage*			0.082
II	54	68.3	
III	49	51.4	
Primary tumor size			0.001
< 5 cm	62	72.00	
≥ 5 cm	41	42.00	
Lymph node metastasis**			0.001
Yes	17	27.50	
No	86	66.20	
Vagina involvement			0.203
None or upper	58	68.50	
Middle	21	51.60	
Lower	24	47.60	
Radiation dose (Gy)			0.002
< 75	29	43.00	
≥ 85	74	67.20	
Radiation proctitis			0.099
None or grade 1	93	59.90	
Grade 2 and above	10	NA	

* II stage: FIGOIIa + IIb, III stage: FIGOIIIa + IIIb.
** Pelvic with or without para-aortic lymph node metastasis.

Multivariate survival analysis indicated that PLN ± PALN (HR = 2.433 95% CI, 1.135–5.215, p = 0.02), primary tumor size (HR = 2.848, 95% CI, 1.443–5.621, p = 0.003), and radiation dose (HR = 0.341, 95% CI, 0.180–0.648, p = 0.001) were independent factors affecting the long-term survival. In contrast, stage, range of vaginal involvement, and radiation proctitis had no impact on long-term survival (Table 4).

Table 4
Multivariate Cox regression analysis of patients.

Clinical factors	p	HR	95.0% CI
Tumor size	0.003	2.848	1.443–5.621
Radiation dose	0.001	0.341	0.180–0.648
Lymph node metastasis*	0.022	2.433	1.135–5.215
Stage	0.829	1.090	0.500–2.375
Vagina involvement	0.878	0.942	0.437–2.029
Radiation proctitis	0.058	1.485	1.078–4.816

* Pelvic with or without para-aortic lymph node metastasis.

4. Discussion

Elderly cervical cancer patients are more likely to have underlying comorbidities that may lead to poor survival, higher toxicity levels, and poor treatment compliance. Therefore, there is a need to identify prognostic factors that may have an impact on survival and treatment-related toxicity.[14] In this study, we evaluated the impact of patient's demographics, tumor stage, RT technique and dose, and underlying comorbidities on OS and toxicity in 103 elderly cervical cancer patients.

Although our study included adenocarcinoma cases (1 mucinous adenocarcinoma and 3 typical types) that tend to have a poor prognosis, overall, our findings indicate a high OS in elderly cervical cancer patients treated with RT. The one, three, and five year OS rates were 96.1%, 67.2%, and 60.2%, respectively. Previously published studies have shown that OS decreases with age. Narayan et al.[12] reported a five-year OS of 65% after RT in patients with a median age of 58 (range from 22–84). Studies reported a five-year OS ranging from 49% to 42% in patients above 75 years old treated with radiotherapy with or without cisplatin-based chemotherapy.[11,16,20] A study by George[13] reported a five-year OS rate of 29% in patients above 85 years of age treated with radiotherapy and ICBT.

Elderly patients are more prone to develop treatment-related toxicity due to a reduction in the normal function of nearby tissue.[15] The incidence of grade III and IV late toxicity in elderly patients with cervical cancer treated with RT ranges from 10% to 20%.[10,16,17,23] In our study, acute GI toxicity occurred in 23 cases and mainly manifested as diarrhea. These side effects were easily relieved with appropriate medications. None of the patients in the study experienced grade III or IV acute GI and bladder toxicity. These findings were consistent with previously published studies by George,[13] Hata et al.,[22] and Kushima et al.,[16] who also reported low levels of GI toxicity in elderly cervical cancer patients treated with RT irrespective of the patient's age or radiation dose.

Vaginal mucositis and perineal dermatitis are common toxicities for patients receiving definitive radiotherapy. A retrospective analysis showed that 25% of gynecological malignant tumor patients who received RT or chemoradiotherapy (CRT) experienced moderate to severe symptoms in the vaginal mucosa at the end of radiotherapy.[35] In our study, burning sensation, pruritus, and pain were the three most common symptoms. The incidence of acute vaginal mucositis and perineal dermatitis was 28.16% and 19.12%, respectively.

Late treatment-related toxicity was low in our study, and only

9.7% of patients developed grade II or above radiation proctitis, and three patients developed grade III myelosuppression. Two patients died as a result of radiation-induced proctitis. One patient suffered from rectovaginal fistula accompanied by tumor progression ten months after completion of the definitive RT. This patient refused further treatment and died 23 months later. Guler et al.[20] reported radiation-induced toxicity in 269 cervical cancer patients above 65 years of age. Three percent of the patients in the study reported rectovaginal fistula, and 1% had a vesicovaginal fistula.

In our study, none of the patients received chemotherapy as part of their treatment. However, the benefit of CRT on survival is still controversial. RT combined with cisplatin-based chemotherapy for locally advanced cervical cancer has a survival benefit.[24] Some studies reported that concurrent CRT improved survival in elderly patients without increasing treatment-related morbidity.[30,31] In contrast, other studies found that CRT failed to reduce the mortality rate in elderly patients with cervical cancer.[26,27] Elderly patients receiving CRT were more likely to experience severe toxicity when compared with younger patients.[25,28,29,31] The main limitation of these studies is the relatively small number of elderly patients included, highlighting the need for further prospective studies to identify the factors that may influence survival in elderly cervical cancer patients treated with CRT.

In our study, multivariate analysis showed that PLN ± PALN, primary tumor size, and radiation dose were identified as independent risk factors for long-term survival. Several studies evaluated the impact of various patient and clinical characteristics on survival. Hata et al.[22] investigated 30 patients above 80 years old with stages IB-IVA squamous cell carcinoma of the uterine cervix treated with RT. Of these 30 patients, 24 received EBRT and ICBT. A total median dose of 69.0 Gy (range 45.6 to 75.4 Gy) was delivered to the cervical tumors. This study identified age and primary tumor size as significant prognostic factors for OS. Ikushima et al.[20] identified the clinical stage as the only significant prognostic factor in elderly patients treated with RT. Lindegaard et al.[23] identified stage and tumor size as independent prognostic factors for tumor control, disease-free survival (DFS), and OS. Guler et al.[20] found that vaginal infiltration and lymph node metastasis were predictive of OS, DFS, local recurrence, and distant metastasis, and patients with tumors larger than 4 cm had a significantly higher risk of developing local recurrence.

Lower radiation doses may not be sufficient to eliminate the tumor, eventually leading to recurrence.[14] In our study, 75 patients completed the RT plan with doses above 85 Gy, and the other 28 patients only completed two-thirds of the treatment. This resulted in a significantly lower five-year OS rate in the patients treated with lower doses. This finding is consistent with the study by Venkatesulu et al.,[25] whereby elderly patients treated with lower radiation doses had a significantly lower five-year OS of 11% compared with a five-year OS of 74% in patients treated with CRT followed by ICBT.

This study has some limitations that have to be acknowledged. The main limitation of this study was the very small sample size, making it difficult to generalize the findings. Another limitation is the inclusion of 4 cases of adenocarcinoma, which the prognosis is worse than that of squamous cell carcinoma, may reduce the statistical power. Furthermore, only 12 patients were treated with IMRT. IMRT can reduce the dose to normal tissue, eventually resulting in fewer side effects and potentially allowing for safe dose escalation.[32] The reduction in toxicity could also allow for better compliance with the treatment and improvement in the quality of life, particularly in elderly patients.[30] Therefore, further research is warranted to evaluate the impact of IMRT on toxicity in elderly patients.

5. Conclusion

Definitive RT resulted in a good OS with acceptable toxicity in elderly cervical cancer patients aged above 75 years, irrespective of their underlying comorbidities. Patients with a primary tumor size above 5.0 cm, PLN ± PALN, and those treated with a radiation dose below 75 Gy had significantly worse OS. However, some patients did not complete the treatment due to toxicities. These findings indicate that in order to ensure compliance with treatment, patients would need to be carefully selected and monitored during treatment to ensure that the side effects are adequately managed. Additional research is needed with a larger sample size to enhance the generalizability and statistical power of the findings. Moreover, there is a need for additional studies to assess the impact of less invasive treatment, such as IMRT, on survival and toxicity.

Acknowledgments

We would like to thank TopEdit (www.topeditsci.com) for the English language editing of this manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Contributions

LHL, LX, and XR contributed to the study design. XR and CGL were responsible for the management of the project and quality assessment. LHL collected and analyzed the patient data and also contributed significantly to writing the manuscript. All authors were involved in the recruitment, treatment, and follow-up of patients. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of Fujian Cancer Hospital in accordance with the Declaration of Helsinki and current ethics guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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