



# Radiation therapy for nonmetastatic medically inoperable upper-tract urothelial carcinoma

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**Background:** The standard management for upper urinary tract urothelial carcinoma (UTUC) is radical nephroureterectomy (RNU). However, some patients cannot undergo this procedure for several reasons, such as unresectable disease, old age, and multiple comorbidities. Our study explored the potential safety and effectiveness of radiotherapy as a curative treatment for UTUC patients unfit for surgery.

**Methods:** The data of patients treated with radiotherapy between December 2017 and November 2019 were retrospectively reviewed. For the literature review, computerized PubMed Medline, Index Medicus, and Web of Science databases and reference lists from the identified publications of interest were used. And “upper-tract urothelial carcinoma” and “radiotherapy” were used as key words in the search.

**Results:** We describe 8 patients with UTUC who were treated with radiotherapy. The median follow-up time was 13.5 months (range, 8.6–30.9 months). Local tumor control was achieved in all patients. However, distant metastases were observed in 2 patients with T3-4/N+ status. One patient had T4 status and the other had N2+ status. The patients died of tumor progression at 15.0 and 17.7 months. In addition, the other 6 patients who were still alive had relatively early-stage tumors without nodal involvement. Regarding acute toxicity, according to the CTCAE v5.0, mild side effects were noted, including grade 1 nausea and diarrhea. Four patients developed mild anemia, generally of grade 1–2. One patient experienced grade 3 anemia, but it was manageable and improved with symptomatic support. In addition, no grade 4 acute or late toxicities were observed. No significant long-term impairment of renal function occurred.

**Conclusions:** For patients with nonmetastatic UTUC who are not suitable for surgery, radiotherapy is a safe treatment and can achieve good local tumor control.

**Keywords:** Upper urinary tract urothelial carcinoma (UTUC); radiation therapy; nonmetastatic; inoperable

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## Introduction

Upper urinary tract urothelial carcinoma (UTUC) is an uncommon disease and accounts for only 5–10% of urothelial carcinoma cases (1,2). However, the incidence of UTUC has been increasing in recent years, and UTUC is generally most prevalent in China and the Balkan region (2). Consumption of aristolochic acid-containing Chinese herbs and Balkan endemic nephropathy are associated with an increased risk of urothelial carcinoma (3–5).

Surgery is the preferred approach for treating nonmetastatic UTUC, and radical nephroureterectomy (RNU) is the mainstay treatment for most patients (2). However, some patients may not be able to undergo surgery because of unresectable disease, old age, multiple comorbidities, and/or severely compromised performance status. UTUC has a peak incidence in individuals aged 70–90 years (6). Unfortunately, for patients unsuitable for surgery, the nonsurgical treatment strategy remains unclear due to a lack of research and effective clinical evidence. Nir Kleinmann reported that intracavitary administration of pyelocalyceal UGN-101, a mitomycin-containing reverse thermal gel, might offer a kidney-sparing treatment alternative (7) but mainly for low-grade upper tract urothelial carcinoma. Therefore, there is no standard treatment for patients with UTUC who are not candidates for surgery.

Radiotherapy has been used to treat patients with cancer for over 100 years. It is an effective tool in the armamentarium against many tumors, including bladder cancer and many other cancers. Radiotherapy is an alternative to cystectomy in patients with muscle-invasive bladder cancer (8–11). Particularly for elderly patients with invasive bladder cancer, radiotherapy can provide excellent results with a high complete response rate and good tolerability (12,13). The main pathologic type of bladder cancer is urothelial carcinoma. Radiotherapy may offer a therapeutic alternative in such patients with UTUC who are unfit for surgery. With the development of radiotherapy technology, the application of volumetric modulated arc therapy (VMAT) can increase the dose in the tumor area to cure tumors while reducing the dose in the organs at risk (OARs), especially the intestines and spinal cord. Iizumi *et al.* found that radiotherapy may be a potential option for patients with UTUC, especially for those unsuitable for radical surgery (14). Consequently, radiotherapy may also be used as a noninvasive radical treatment to improve survival for such patients.

To date, in our institution, 8 patients who were unfit for surgery have been treated with VMAT. Our study reviews

the cases of UTUC patients who were unfit for surgery and received radiotherapy and reviews the literature on this topic. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tau-21-291>).

## Methods

### *Patient selection*

From December 2017 to November 2019, a total of 8 patients with UTUC were treated with radiotherapy at the Peking University First Hospital and these cases were retrospectively analyzed. Computed tomography (CT) was performed on patients to confirm the location of the tumor and the absence of evidence of malignancy in the bladder and urethra. And 5 of 8 patients performed Cystoscopy or <sup>18</sup>F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT. Most patients refused to undergo invasive testing, such as ureteroscopic histologic biopsy. However, they underwent urine cytology testing, and 3 patients' urinary cytology results were positive for urothelial carcinoma. All patients underwent CT urography. Two experienced radiologists independently evaluated the scans to ensure that all medical images had minimal heterogeneity in the diagnosis, and disagreements were resolved by consensus (15).

Routine clinical staging included a complete medical history, physical examination, CT, PET/CT (if perfected). No patients exhibited evidence of distant metastatic disease. All patients were staged according to the 8th edition of the Union for International Cancer Control and American Joint Committee on Cancer (UICC/AJCC) staging system. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethical committee of Peking University First Hospital (No.: 2016-1253) and individual consent for this retrospective analysis was waived.

### *Treatments and follow-up procedures*

Before radiotherapy, the recruited patients underwent a CT scan (Big Bore 16-row helical CT with a 5-mm thick layer image reconstruction; Philips, Amsterdam, Netherlands) of the treatment area for planning purposes. A Synergy linear accelerator (6-MV photons, 60-pair multilobed grating; Elekta, Stockholm, Sweden) or a Trilogy linear accelerator (6-MV photons, 60-pair multilobed grating; Varian, Palo

**Table 1** Baseline clinical characteristics of patients

No	Age (years)	Sex	KPS	Site	Size (cm)	TNM	Risk	RT fractionation	BED	Reason
1	84	M	70	Renal pelvis	2.7	T3N0M0	High	SABR (24 Gy/3 fr) + CRT (52.8 Gy/22 fr)	108.7 Gy	Refusal of surgery
2	60	M	70	Renal pelvis	3.2	T1/2N0M0	High	SABR (30 Gy/5 fr) + CRT (48 Gy/20 fr)	107.5 Gy	Medically inoperable
3	78	F	80	Renal pelvis	2.6	T1/2N0M0	High	SABR (24 Gy/3 fr) + CRT (52.8 Gy/22 fr)	108.7 Gy	Medically inoperable
4	89	F	70	Ureter	8.6	T4N0M0	High	SABR (30 Gy/5 fr) + CRT (48 Gy/20 fr)	107.5 Gy	Medically inoperable
5	76	M	70	Ureter	1.1	T1/2N0M0	Low	CRT (62.5 Gy/25 fr)	78.1 Gy	Medically inoperable
6	81	M	90	Ureter	3.3	T3N2M0	High	CRT (62.5 Gy/25 fr)	78.1 Gy	Refusal of surgery
7	94	M	80	Ureter	5.1	T1/2N0M0	High	CRT (60 Gy/25 fr)	74.4 Gy	Refusal of surgery
8	84	M	90	Ureter	2.4	T2/3N0M0	High	CRT (67.5 Gy/25 fr)	85.7 Gy	Refusal of surgery

RT, radiotherapy; SABR, stereotactic ablative boost radiotherapy; BED, biologically equivalent dose; CRT, conventionally fractionated radiotherapy

Alto, CA) was used. Patients were immobilized with the thermoplastic film. All patients underwent image-guided VMAT (IG-VMAT) and daily cone-beam computerized tomography (CBCT) to ensure accuracy of the position and reduce errors.

### Radiotherapy technique

The gross tumor volume (GTV), comprising the known extent of disease (primary and nodal) on imaging (CT/PET-CT). The clinical target volume (CTV) includes regions of presumed microscopic extent or dissemination. The planning target volume (PTV) consisted of the CTV with a 5 mm margin expansion. There are two strategies for radiotherapy: partial stereotactic ablative boost radiotherapy (p-SABR) and conventionally fractionated radiotherapy (CRT). When the tumor was located in the renal pelvis and upper ureter, most patients were treated with p-SABR regimen because it's farther from the intestine. However, when the tumor was located in the middle and lower ureter, the CRT protocol was chosen and the field of CTV extended, including the adjacent ureteral passage region and the lymphatic drainage region.

Half of the 8 patients underwent the p-SABR regimen, which consisted of two phases. The focus of the p-SABR regimen is sequential dose administration, with SABR as the first stage of radiotherapy followed by the second stage of CRT. The SABR component delivered a GTV dose of 24–30 Gy in 3–5 fractions, and the subsequent CRT component delivered a dose of 40–52.8 Gy in 20–22 fractions. The total GTV dose was approximately

76.8–78 Gy. When assuming an  $\alpha/\beta$  ratio of 10, the biological equivalent dose (BED<sub>10</sub>) of the tumor was 107.5–108.7 Gy. The PTV dose was approximately 50–60 Gy in 25 fractions. The other 4 patients underwent the CRT regimen, which included delivery of a prescribed GTV dose ranging from 60 to 67.5 Gy and a PTV dose of 45–50 Gy in 25 fractions. The mean BED<sub>10</sub> of the tumor was 78.1 Gy (74.4–85.7 Gy) (Table 1). During the SABR component, the dose in OARs decreased to approximately 3 Gy/f. The total dose limit of OARs was within the safe range specified in the Radiation Therapy Oncology Group (RTOG) standard.

### Follow-up procedures

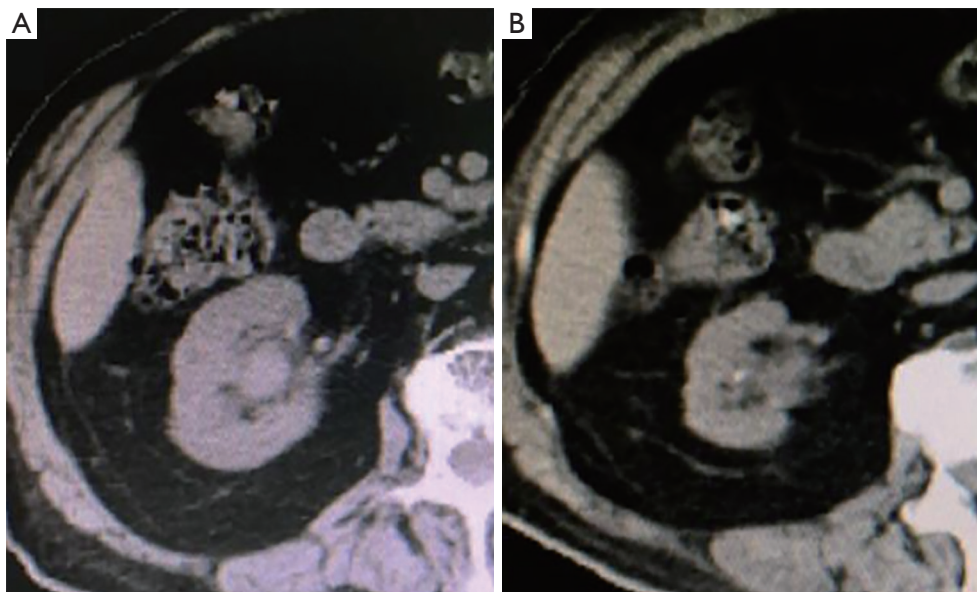
All patients were followed up at 3–6 months intervals after VMAT or until death, with intervals extending to 6–12 months after 2 years. Physical examination, CT and blood routine and renal function examination were needed. Toxicity was graded by the patient's treatment team according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.

### Literature review and statistical analysis

An extensive review of the literature on UTUC patients unfit for surgery who received radiotherapy was performed using the PubMed Medline, Index Medicus, and Web of Science databases and the reference lists from the identified publications of interest (review articles, case reports). “Upper-tract urothelial carcinoma” and “radiotherapy”

**Table 2** Treatment outcomes of patients

No	Local recurrence	Distant metastasis	Metastasis site	Time to metastasis (months)	Death	Survival (months)
1	No	No	–	–	No	8.6
2	No	No	–	–	No	30.9
3	No	No	–	–	No	11.0
4	No	Yes	Lung	13.5	Yes	15.0
5	No	No	–	–	No	28.1
6	No	Yes	Liver	11.0	Yes	17.7
7	No	No	–	–	No	12.0
8	No	No	–	–	No	9.4

**Figure 1** CT images after radical radiotherapy (case 1). The right renal pelvis tumor 1 week before and 3 months after RT. RT, radiotherapy.

were used as key words in the search. The clinical baseline data of the patients, mainly including sex, age, tumor site, clinical stage, radiation fractionation and field, and eventual multiplicity, were recorded and analyzed when available.

## Results

The patient characteristics and treatments are summarized in *Table 1*. The primary tumor sites included the ureter (n=5) and renal pelvis (n=3). The average age was 80.75 years (range, 60 to 94 years). All patients were treated with radiotherapy alone, without any systemic therapy. The median follow-up time was 13.5 months (range,

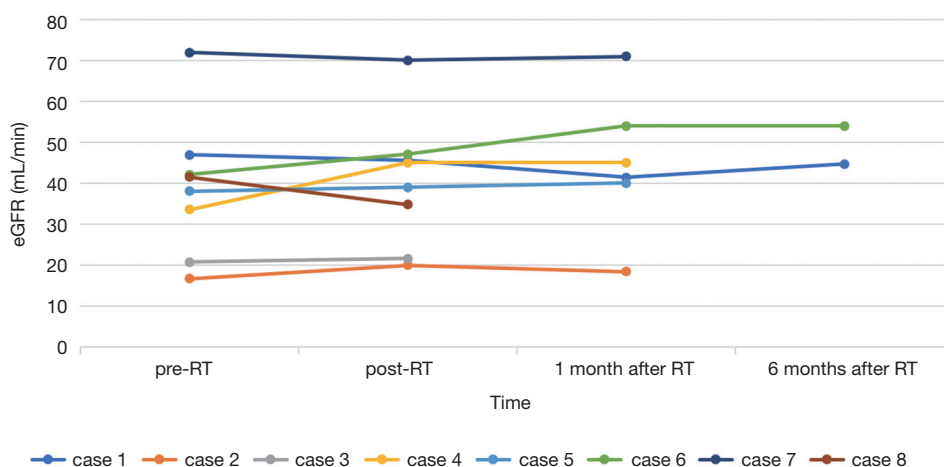
8.6–30.9 months). The median BED<sub>10</sub> was 96.6 Gy.

Local tumors were well controlled in all patients. Distant visceral metastasis occurred at 13.5 and 11.0 months in 2 patients. One patient had T4 status and the other had N2+ status. The 2 patients both died of tumor progression at 15.0 and 17.7 months. The other 6 patients had no disease progression and no recurrence or distant metastasis. At the last follow-up, the remaining 6 patients were still alive without disease progression (*Table 2*). After radiotherapy, local tumors can be well controlled, as shown in *Figure 1*. Ureteral stricture due to tumor mass could also be relieved under tumor control.

During the follow-up, in terms of acute toxicity, mild

**Table 3** Summary of treatment morbidities

No	Acute		Late [grade]
	Hematological [grade]	Nonhematological [grade]	
1	Anemia [3]	None [0]	Anemia [1]
2	None	Nausea [1]	None
3	Anemia [2]	Diarrhea [1]	None
4	Anemia [2]	Nausea [1]	Anemia [1]
5	None	Diarrhea [1], urinary frequency [1]	None
6	Anemia [1]	None	None
7	Anemia [1]	None	None
8	None	None	None



**Figure 2** The eGFR before and after radiation for all patients with UTUC. eGFR, estimated glomerular filtration rate; RT, radiotherapy; UTUC, upper urinary tract urothelial carcinoma.

side effects were noted, including grade 1 nausea and diarrhea. Four patients developed mild anemia, generally of grade 1–2. One patient experienced grade 3 anemia, but it was manageable and improved with symptomatic support. In addition, no grade 4 toxicities were observed. With respect to late toxicities, we observed no serious radiation-associated injuries (Table 3). There was no significant long-term impairment of renal function and no ureterostenosis occurred (Figure 2).

**Literature review**

According to the literature, 9 patients with UTUC who underwent radiotherapy and did not receive surgery were

described in 3 publications (14,16,17) (Table 4). In terms of the radiotherapy strategies used, two of the studies used photons, and one used proton.

**Discussion**

A new noninvasive treatment model is necessary for patients with UTUC who are medically inoperable. Radiotherapy plays a very important role in the treatment of urothelium carcinoma. Based on the above literature, radiotherapy can serve as a safe and effective noninvasive treatment for patients with nonmetastatic UTUC who cannot tolerate or refuse surgery.

Additionally, UTUC that invades the muscle wall usually

**Table 4** Radiotherapy for nonmetastatic, medically inoperable, UTUC: review of published cases

Case No and reference	Age (years)	Sex	Location	Size (cm)	TNM	Risk	RT fractionation	Chemotherapy	Time to progression (months)
Maehata <i>et al.</i> (17)	87	F	Ureter	–	T2N0M0	–	60 Gy/10 fr	No	12
	87	M	Ureter	–	T2N0M0	–	50 Gy/10 fr	No	12
	85	F	Ureter	–	T2N0M0	–	60 Gy/10 fr	No	24
Evans <i>et al.</i> (16)	95	M	Renal pelvis	4.5	T2N0M0	High	50 Gy/4 fr	No	–
Iizumi <i>et al.</i> (14)	72	M	Renal pelvis	3	T1/2N0M0	High	72.6 Gy/22 fr	No	–
	85	–	Renal pelvis	2	T1/2N0M0	High	72.6 Gy/22 fr	No	36
	59	–	Ureter	25	T3N2M0	High	66 Gy/33 fr	Yes	1
	80	M	Ureter	3	T1/2N0M0	High	66 Gy/33 fr	No	48
	64	–	Renal pelvis	4	T4N2M1	High	66 Gy/33 fr	Yes	28
Present series	84	M	Renal pelvis	2.7	T3N0M0	High	SABR (24 Gy/3 fr) + CRT (52.8 Gy/22 fr)	No	–
	60	M	Renal pelvis	3.2	T1/2N0M0	High	SABR (30 Gy/5 fr) + CRT (48 Gy/20 fr)	No	–
	78	F	Renal pelvis	2.6	T1/2N0M0	High	SABR (24 Gy/3 fr) + CRT (52.8 Gy/22 fr)	No	–
	89	F	Ureter	8.6	T4N0M0	High	SABR (30 Gy/5 fr) + CRT (48 Gy/20 fr)	No	13.5
	76	M	Ureter	1.1	T1/2N0M0	Low	CRT (62.5 Gy/25 fr)	No	–
	81	M	Ureter	3.3	T3N2M0	High	CRT (62.5 Gy/25 fr)	No	11.0
	94	M	Ureter	5.1	T1/2N0M0	High	CRT (60 Gy/25 fr)	No	–
84	M	Ureter	2.4	T2/3N0M0	High	CRT (67.5 Gy/25 fr)	No	–	

RT, radiotherapy; SABR, stereotactic ablative boost radiotherapy; CRT, conventionally fractionated radiotherapy; UTUC, upper urinary tract urothelial carcinoma.

has a poor prognosis. Several retrospective reviews have reported that the locoregional failure rate varies from 6.2% to 46.3% in UTUC patients who undergo RNU (18-20). The 5-year cancer-specific survival (CSS) is <50% for pT2/pT3 and <10% for pT4 UTUC (21-23). In our study, local tumors were well controlled in all patients. Although our follow-up time was not sufficiently long, local tumor control was still effective compared with that in previously reported studies. According to our retrospective analysis of the previous literature and a summary of previously reported cases, similar supporting conclusions can be drawn. The results of the analysis show that radiotherapy is beneficial for local tumor control in patients with nonmetastatic UTUC.

In terms of the radiation dose and fraction, the median

BED<sub>10</sub> in this study was similar to that in previous studies (96.6 vs. 96 Gy), most of which used limited field exposure, suggesting that the radiotherapy dose used in this study can achieve good local control.

In the current study, no local recurrence was observed until the last follow-up in the 8 patients, while the main measure for failure was distant metastasis. Previous studies have reported that systemic recurrences are frequent and lethal in advanced ( $\geq$ pT3) UTUC stages (24). The 5-year CSS rate of patients with early-stage ( $\leq$ pT2N0) UTUC treated with RNU is fair (74.7%); in contrast, the rates are decreased in patients with advanced disease (pT3, 54.0% and pT4, 12.2%) or nodal involvement (35.5%) (25). Specific poor prognosis factors mainly include older age, poor



performance status, tobacco consumption, hydronephrosis, high tumor stage and grade, and lymphatic metastasis (2). In our study, most of the enrolled patients were older, with an average age older than 80 years, and these patients had many poor prognostic factors. The two patients who died of tumor progression in this study also had advanced age and a high T/N+ stage. Local tumor control was achieved in all patients. Compared to the results of previous studies, these results indicate that radiotherapy can benefit local tumor control, but distant metastasis is the main reason for failure.

Regarding safety, two individual studies published in the last few years were case reports of the use of stereotactic body radiotherapy (SBRT) for the treatment of UTUC. Maehata and Evans both reported their experience using SBRT in elderly patients with medically inoperable UTUC, and no acute or late adverse events were observed in any of the three cases (16,17). In the present study, our cases supported the clinical experience of Maehata and Evans. During treatment and follow-up, the plans were completed on schedule, and no severe acute or late complications were observed, even though 3 of the 8 patients were treated using extended radiotherapy fields. More specifically, no acute or late toxicities above grade 3 were observed, and although anemia and gastrointestinal discomfort were common, the cases were generally mild, with no significant impact on quality of life. Regarding renal function, there was no obvious impairment in the patients who could be observed. On the one hand, the reason may be that the tumor in most cases was located in the ureter and that the radiation dose to the kidney was low. However, longer follow-up periods are needed. In addition, no stricture was found during radiotherapy in our study or in previous reports. Some possible reasons are that the doses given in our current study are safe, with a very low probability of inducing stenosis, or that our follow-up time was not sufficiently long. On the other hand, in the case of UTUC, the small intestine is close to the ureter. Previously, it was very difficult for conventional radiotherapy to achieve a radical dose in the tumor area due to the dose limitation of normal tissues such as the small intestine. However, recent advances in radiotherapy technology have provided strategies that enable sparing of OARs from high doses of treatment, and the application of daily image guidance technology can also help reduce errors. Overall, our data have provided evidence that radiotherapy may be a safe radical treatment for patients with UTUC who are unfit for surgery.

Given the recent POUT results (26), adjuvant platinum-based chemotherapy should be considered as a new standard

of care after nephroureterectomy for patients with UTUC. Therefore, the potential role of chemotherapy in medically inoperable UTUC may be worth studying in the future. Immunotherapy targeting the PD-1/PD-L1 pathway has had good effects in treating urothelial tumors (27). It has been reported that radiotherapy has the potential to synergize with immunotherapy to improve oncological outcomes in patients with urothelial muscle-invasive bladder cancer (28). PD-L1 expression on tumor cells independently predicted shorter CSS in UTUC (29). Thus, the application of radiotherapy combined with immunization in UTUC may be a direction worthy of future exploration.

There were several limitations of this case report. First, 4D breath-gating techniques may be needed because the movement of the kidneys may vary with the degree of breathing motion. Second, the staging and diagnosis of UTUC were based on clinical findings and not pathological findings. Third, this report was a retrospective study. The durations of observation in this study were short, and the number of cases was small. Further studies including a larger number of patients are also needed. A longer observation period may be needed to more accurately estimate late adverse events.

## Conclusions

For patients with nonmetastatic UTUC who are not suitable for surgery, radiotherapy is a safe treatment and can achieve good local tumor control. Future research should be conducted to confirm these results.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/tau-21-291>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethical committee of Peking University First Hospital (No.: 2016-1253) and individual consent for this retrospective analysis was waived.

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