Oncology and Translational Medicine

Volume 4 • Number 3 • June 2018

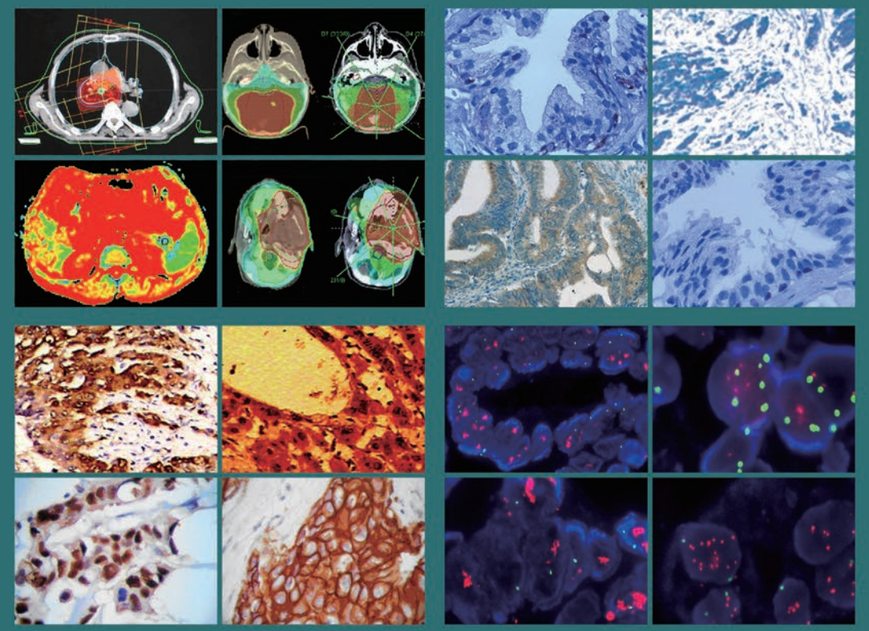
Oncology and Translational Medicine Volume 4 • Number 3 • June 2018 pp 85–131

邮发代号：38-121
ISSN 2095-9621

GENERAL INFORMATION
≫otm.tjh.com.cn

ISSN 2095-9621
CN 42-1865/R

Oncology and Translational Medicine



Volume 4
Number 3
June 2018

Oncology and Translational Medicine

Oncology and Translational Medicine
June 2018 Volume 4 Number 3

Contents

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0261-1

June 2018, Vol. 4, No. 3, P85–P92

ORIGINAL ARTICLE

Postoperative sequential chemotherapy and radiotherapy for locally advanced gastric cancer

Qiang Fu[1], Shiying Yu[1], Guoqing Hu[1], Yuan Chen[1], Junbo Hu[2], Lihong Zhang[1], Hong Qiu[1], Xianglin Yuan[1] (✉)

[1] Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[2] Department of Gastrointestinal Surgery, Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract

Objective The aim of the study was to evaluate the role of postoperative sequential chemotherapy and radiotherapy in patients with locally advanced gastric cancer.

Methods From January 2003 to December 2010, 146 gastric cancer patients at our institution (Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) received postoperative sequential chemotherapy and radiotherapy after radical surgery. Radiotherapy was administered as a dose of 4500 cGy in 25 fractions. For patients with positive margins, the dose was raised to 5040 cGy in 28 fractions. Three cycles of mFOLFOX or PF (cisplatin, 5-fluorouracil) chemotherapy regimen were applied before and after radiotherapy. Three- and 5-year survival rates were analyzed; any adverse effects with respect to hematology, hepatic and renal function, or the gastrointestinal tract that occurred during the treatment were evaluated.

Results This cohort consisted of non-metastatic patients: 104 men and 42 women with a median age of 51.0 years. The full course of sequential chemotherapy and radiotherapy (4500–5040 cGy) was completed by 129 patients (88.4%). Seventeen regional relapses (9.8%) and 46 distant relapses (23.8%) were recorded. Fifty patients (34.2%) died during follow-up. The 3- and 5-year overall survival rates (OS) were 60% and 54%, and disease-free survival rates (DFS) were 53% and 47%, respectively. There were no significant differences in survival rate with respect to age, sex, histopathology, N stage, site of the tumor, or margin status. Multivariate analysis showed that only the depth of tumor invasion (T stage) was an independent prognostic factor for OS (P = 0.009) and DFS (P = 0.006). The rates of grades 3 and 4 neutropenia and vomiting were 9.6% and 3.4%, respectively, during the treatment.

Conclusion Postoperative sequential chemotherapy with an mFOLFOX or PF regimen and radiotherapy were found to be an effective means of treating advanced gastric cancer patients with T3–T4 disease. The adverse effects of this treatment were tolerable.

Received: 22 March 2018
Revised: 16 April 2018
Accepted: 20 May 2018

Key words: advanced gastric cancer; sequential chemotherapy; radiotherapy; survival rate

Gastric cancer ranks second among the most common cancers with respect to morbidity rate and third with respect to the mortality rate in China. In 2015, approximately 679 100 new upper gastrointestinal cancer cases were reported in China, and these were responsible for 498 000 deaths [1]. China is a high-incidence area for gastric cancer, and the situation shows no sign of improvement except in a few local areas. The mortality rate of gastric cancer can be attributed contributes more to more than 20% of all the cases of cancer metastasis in China [2]. Complete surgical resection is currently the most effective and potentially curative treatment available to patients with gastric cancer; however, only 25%–40% of first-time gastric cancer patients are eligible for radical surgery [3]. The overall 5-year survival rate has been only 20%–30% over the past 30 years [4–5].

Even after complete resection with negative margins, the risk of T3–4 and N1–3 local recurrence (local lymph node, peritoneum) remains high. Postoperative chemotherapy showed benefits for Asian patients; however, the recurrence rate was not reduced. This suggests that it is important to consider postoperative

✉ Correspondence to: Xianglin Yuan. Email: xlyuan1020@163.com

adjuvant therapy for patients with gastric cancer. In the INT0116 studies, postoperative chemoradiotherapy was shown to reduce local recurrence and promote survival [6–8]. In these studies, more than 90% of the patients were treated with D0- or D1-resection, but some studies have shown that chemoradiotherapy (CRT) can also decrease the rate of local recurrence in patients with D2-resection. The recently updated analysis of the INT0116 reveals that adjuvant CRT also potentiates the treatment benefit on overall survival (OS) in a subset of patients with D2 dissection [9], similar to a Korean retrospective study [10]. In the ARTIST trial [11], the largest phase III trial comparing CRT versus chemotherapy in patients with D2 gastrectomy, no statistical difference in 3-year disease-free survival (DFS) was observed between the two arms. Furthermore, the addition of radiotherapy (RT) to chemotherapy did not positively impact the pattern of relapse (locoregional or distant). In a subgroup analysis of 396 patients with positive pathologic nodes, however, there was a significant prolongation of 3-year DFS for CRT over chemotherapy (77.5% vs. 72.3%; P = 0.0365). However, a recent meta-analysis showed that postoperative CRT could benefit the survival of gastric cancer patients, especially regarding 5 year DFS, independent of surgical procedure [12]. Therefore, many controversies remain over the role of RT for gastric cancer after surgery.

With the latest clinical data providing convincing evidence of the link between D2 dissection and lower recurrence rates in patients with resected gastric cancer, both the European Society for Medical Oncology and the US National Comprehensive Cancer Network (NCCN) have recommended D2 dissection for those patients, leading to a worldwide consensus [13–14]. However, due to the difference between Eastern and Western surgical methods and the race of the patients, it has been difficult to determine which treatment is the most beneficial. Although the INT0116 trial was initiated in the early nineties, the concept of concurrent CRT has not become widespread in China. The biggest obstacle to its application comes from its adverse hematological and gastrointestinal effects. In the INT0116 study, 17% of the patients did not complete the treatment because of side effects [6]. As our previous studies showed, the adverse effects of postoperative sequential CRT were no greater than those of chemotherapy alone [15]. Therefore, we have designed a postoperative CRT sequence, aimed at reducing toxicity while maintaining curative effects similar to concurrent CRT.

Patients and methods

This is a retrospective analysis of a series of patients identified in our database from Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Between January 2003 and December 2010, 168 patients with pathologically confirmed adenocarcinoma of the gastroesophageal junction or stomach were treated with sequential chemotherapy and RT. Among them, 146 patients who underwent surgery with curative intent received adjuvant sequential chemotherapy and RT, and 22 patients received palliative CRT. The patients included in this study met the following criteria: staging done according to the 7th edition of the American Joint Commission on Cancer Staging Manual; no metastatic disease; Eastern Cooperative Oncology Group performance status (PS) score of 0–1; serum creatinine (mg/dL) ≤ 1.5× the upper limit of normal; total bilirubin (mg/dL) ≤ 1.5× the upper limit of normal; alanine aminotransferase ≤1.5× the upper limit of normal; and no preoperative chemotherapy. Treatment began as soon as possible and no later than 4 weeks after surgery. The pretreatment evaluations included physical examination, tumor markers, and computed tomography (CT) to rule out metastatic disease.

In our investigation, 146 patients received the regimen of RT and sequential chemotherapy. Chemotherapy consisting of oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (mFOLFOX) was administered to 113 patients. Chemotherapy consisting of 5-FU/cisplatin (PF) was administered to 33 patients during the same treatment period. Postoperative CRT was performed sequentially after surgery. First, three cycles of chemotherapy were administrated to patients, followed by radiotherapy. Subsequently, the patients underwent another three cycles of chemotherapy.

Postoperative chemotherapy regimen: The mFOLFOX regimen was as follows: oxaliplatin 130 mg/m^2 d1; 5-FU 425 mg/m^2 d1–5; leucovorin 200 mg/m^2 d1–5 every 3 weeks. The PF regimen was as follows: cisplatin 80 mg/m^2 d1; 5-FU 800 mg/m^2 d1–5 every 3 weeks.

Radiotherapy was delivered following the recommendations outlined in INT0116 [11]. All patients were treated using a standardized 3D conformal technique. When available, the preoperative and postoperative scans and endoscopic, surgical, and pathological reports were reviewed. Patients had CT simulations performed at least 1 week before the beginning of radiotherapy. The CT simulation slice thickness was 5 mm. Patients were scanned in the supine position with their arms above their heads. A total radiation dose of 45 Gy was delivered in 25 fractions at 1.8 Gy per fraction, 5 days per week over 5 weeks. The patients with positive margins were given booster doses of 5.4 Gy to a total radiation dose of 50.4 Gy. Dose variation in the planning target volume (PTV) was kept within +7% and –5% of the prescribed dose in accordance with ICRU 50/62 recommendations.

Radiation was delivered using 6–15 MV photons with a linear accelerator. The clinical target volume (CTV) and the design of the radiation treatment fields were individualized depending upon the extent and location of the primary tumor and involved lymph nodes and on the type of surgery performed. Lymph node stations in the radiation fields included perigastric, coeliac, splenic hilar, suprapancreatic, porta hepatis, pancreaticoduodenal, and local paraaortic nodes. In patients with tumors of the gastroesophageal junction, paracardial and paraesophageal lymph nodes were included in the radiation fields, but pancreaticoduodenal radiation was not required. The PTV consisted of the CTV with a 1-cm margin. The organs at risk were contoured, which included the kidneys, liver, heart, and spinal cord. At least two-thirds of one kidney was spared. No more than 30% of the heart received more than 40 Gy, and no more than two-thirds of the liver received more than 30 Gy. The maximum spinal cord dose was less than 45 Gy. A dose-volume histogram was used to ensure that the dose tolerances were met for the nearby critical organs.

Acute toxicity data were graded according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria. Hematologic toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3. Postoperative follow-up by the treating oncologist was scheduled every 3 to 6 months for the first 2 years and every 6 months thereafter. Follow-up included taking detailed patient histories and performing physical examinations. Neither routine endoscopy nor CT scans (chest, abdomen, or pelvis) were performed unless clinically warranted. Patients were followed with routine complete blood count (CBC), chemistry, carcinoembryonic antigen (CEA), and CA 19-9 at every follow-up (as per GAST-5 NCCN guidelines). Sites of first failure (locoregional or distant) were also documented.

Locoregional recurrence was defined as any recurrence in the tumor bed, anastomosis site, gastric remnant, duodenal stump, or regional nodes within the irradiated volume.

Distant metastases were defined as any recurrence outside of the irradiated field, including metastases to the liver, lower paraaortic lymph nodes, and extra-abdominal sites, and peritoneal seeding. DFS was measured from the date of radical surgery to the date of the first recurrence of the disease. OS was also recorded from the date of radical surgery until death from any cause.

Statistical analysis

The data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL). Patient survival was calculated using the Kaplan-Meier method. To assess the importance of potential prognostic factors, we performed univariate and multivariate analyses using log-rank testing and a Cox proportional hazards regression model. *P*-values < 0.05 were considered significant.

Results

The cohort consisted of 146 patients; 104 men and 42 women. Patient and tumor characteristics are outlined in Table 1. The mean age was 51.0 years (range, 24–66 years) and the median age was 50.0 years. All of the patients had a PS score of 0 or 1. Hundred and twelve (76.7%) underwent subtotal gastrectomy, and 34 underwent total gastrectomy (23.3%). Hundred and thirty-one patients (89.7%) had negative margins, whereas 15 had infiltrated surgical margins. Hundred and seventeen patients (81.3%) had T3–T4 primary tumors. Ninety-three patients (76.2%) had regional nodal involvement. Thirty-four patients had a D1 nodal clearance, and 112 patients had D2 surgery. Refer to Table 1 for detailed patient characteristics.

Table 1 Characteristics of patients selected

Characteristics	No.	%
Sex		
Male	104	71.2
Female	42	28.8
Median age (range, years)	51 (24–66)	
Pathological type		
Well differentiated adenocarcinoma	11	7.5
Moderately differentiated adenocarcinoma	21	14.4
Poorly-undifferentiated differentiated adenocarcinoma	114	78.1
Surgery		
Subtotal gastrectomy	112	76.7
Total gastrectomy	34	23.3
Tumor location		
Gastroesophageal junction (cardia)	38	26.0
Gastric body	24	16.4
Antrum / pylorus	76	52.1
The broader areas beyond the range of the above requirements	8	5.5
Lymph node dissection		
D1	34	23.3
D2	112	76.7
pT stage*		
T1	10	6.9
T2	18	13.0
T3	85	58.2
T4	32	21.9
pN stage*		
N0	32	21.9
N1	28	19.2
N2–3	86	58.9
Margin		
R0	131	89.7
R1	15	10.3

*According to AJCC staging manual (seventh edition)

As of December 2016, the median follow-up was 47.5 months. Twenty patients were lost to follow-up, and the follow-up ratio was 86.3%. The full course of CRT was completed by 129 patients (88.4%). Of the patients who could not complete the sequence as planned, 17 patients interrupted it for grade 4 gastrointestinal toxicity. Fifteen patients with positive margins were administered the booster dose of 540 Gy and a total radiation dose of 5040 Gy. Thirty-three and 113 patients received PF and mFOLFOX, respectively. Acute toxicity was recorded during the CRT regimen and throughout the adjuvant chemotherapy cycles (Table 2). The most common acute adverse effect was gastrointestinal side effects in 103 patients (70.5%) with only 3.4% experiencing grade 3 or 4 toxicity. Hematologic toxicity was the second most common side effect, with 9.6% of patients developing grade 3 or 4 neutropenia. Six episodes of febrile neutropenia were recorded.

Among the total 146 patients in the cohort, 63 (43.1%) experienced relapse during the follow-up period. Isolated locoregional recurrence was observed in 17 patients and relapsed distant disease in 46 patients. One hundred and four patients were followed up for survival. The median OS time has not yet been reached for the entire cohort. Fifty patients (34.2%) died during follow-up. All 48 patients who experienced relapse died. Two patients died during remission, probably due to renal failure. The 3-year and 5-year OS rates were 60% and 54%, and DFS rates were 53% and 47%, respectively (Fig. 1). There were no significant differences in 5-year survival rate after postoperative CRT with respect to age, sex, history, pathology, N stage, tumor location and size, lymph node dissection, or the presence of a positive incisal margin (Tables 3 and 4). By multivariate analysis, only the depth of tumor invasion (T stage) remained a statistically significant factor for survival (Fig. 2).

Table 2 Acute toxicity of sequence chemoradiotherapy (*n*)

Acute toxity	Sequence chemoradiotherapy group			
	I (%)	II (%)	III (%)	IV (%)
Leucopenia	60 (41.1)	14 (9.6)	11 (7.5)	2 (1.4)
Neutropenia	68 (46.6)	10 (6.8)	12 (8.2)	2 (1.4)
Anemia	9 (6.2)	15 (10.3)	4 (2.7)	0 (0)
Thrombocytopenia	0 (0)	6 (4.1)	5 (3.4)	0 (0)
Nausea, vomiting	58 (31.5)	40 (27.4)	4 (2.7)	1 (0.7)
Liver function	11 (7.5)	2 (1.4)	2 (1.4)	0 (0)
Kidney function	0 (0)	1 (0.7)	2 (1.4)	0 (0)

Table 3 Cox model analysis for OS

	B	SE	Wald	*P*	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Age	–0.090	0.393	0.053	0.818	0.914	0.423	1.975
Gender	–0.291	0.332	0.771	0.380	0.747	0.390	1.432
Smoking history	–0.249	0.375	0.442	0.506	0.779	0.374	1.625
Drinking history	–0.543	0.427	1.621	0.203	0.581	0.252	1.340
Pathology	0.101	0.282	0.128	0.721	1.106	0.636	1.921
Tumor location	0.003	0.168	0.000	0.985	1.003	0.722	1.394
Tumor size	0.105	0.150	0.490	0.484	1.110	0.828	1.489
Lymph node dissection	–0.455	0.387	1.386	0.239	0.634	0.297	1.354
pT stage	0.551	0.212	6.760	0.009	1.736	1.145	2.630
pN stage	0.085	0.138	0.379	0.538	1.088	0.831	1.426
Margin	0.823	0.432	3.630	0.057	2.277	0.977	5.307

Table 4 Cox model analysis for DFS

	B	SE	Wald	*P*	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Age	0.034	0.362	0.009	0.925	1.035	0.509	2.102
Gender	0.057	0.306	0.034	0.853	1.058	0.581	1.928
Smoking history	0.031	0.312	0.010	0.920	1.032	0.560	1.901
Drinking history	–0.647	0.352	3.384	0.066	0.524	0.263	1.043
Pathology	0.182	0.255	0.505	0.477	1.199	0.727	1.978
Tumor location	0.128	0.155	0.686	0.408	1.137	0.840	1.539
Tumor size	0.078	0.137	0.328	0.567	1.081	0.827	1.413
Lymph node dissection	–0.232	0.313	0.552	0.458	0.793	0.429	1.463
pT stage	0.545	0.200	7.447	0.006	1.724	1.166	2.550
pN stage	0.171	0.128	1.784	0.182	1.186	0.923	1.525
Margin	0.661	0.397	2.775	0.096	1.936	0.890	4.212

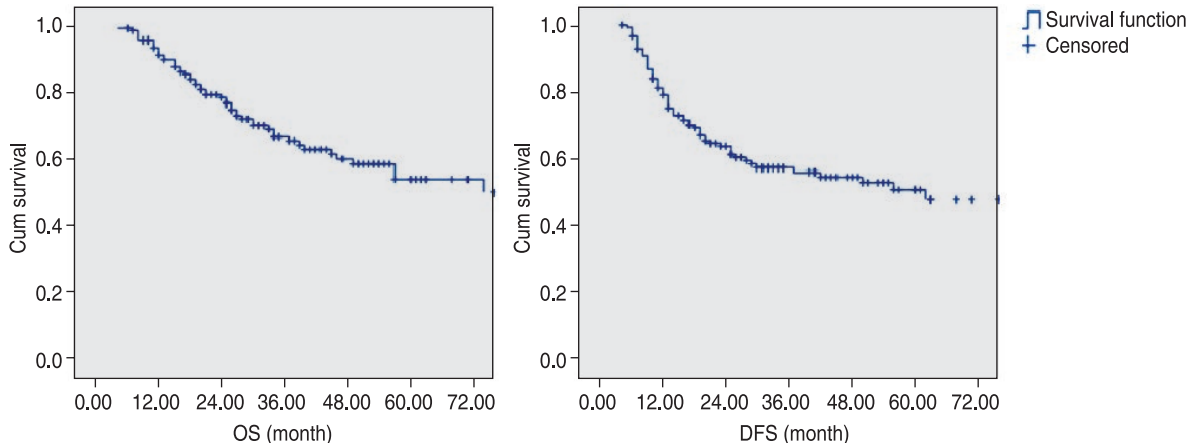


Fig. 1 OS and DFS of 146 patients with advanced gastric cancer. The 3-year and 5-year OS were 60% and 54% and DFS were 53% and 47%, respectively.

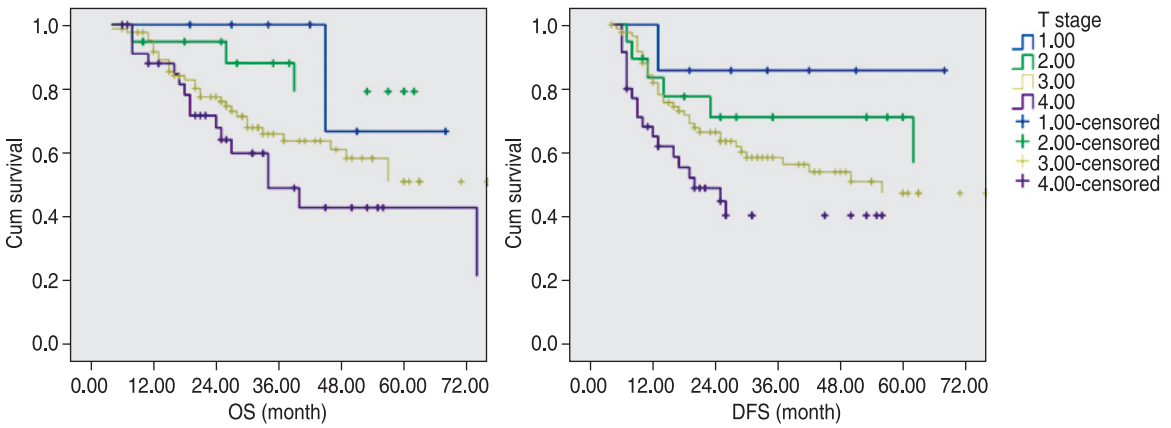


Fig. 2 Comparision of OS and DFS in the subgroup of patients with T stage. Depth of tumor invasion (T stage) was the independent prognostic factors for OS (P = 0.009) and DFS (P = 0.006).

Discussion

Currently, the benefits of adjuvant therapy for gastric adenocarcinoma are disputed due to conflicting results from trials. Western studies have shown that it offers either no or minimal benefits. Hermans *et al* analyzed 11 relevant randomized trials from 1980 to 1991 in which postoperative adjuvant chemotherapy was compared to surgery alone for patients with gastric cancer [odds ratio (OR) = 0.88; 95% confidence interval (CI), 0.78 to 1.08] [16]. They concluded that postoperative chemotherapy, in general, offers no additional survival benefit for patients. Earle *et al* revisited a meta-analysis of 13 randomized trials in non-Asian countries and found that adjuvant chemotherapy may produce a small survival benefit with borderline statistical significance [17]. In a randomized trial in Japan that analyzed studies of stage II and III gastric cancer (ACTSGC), patients underwent extended (D2) lymph node dissection followed by adjuvant therapy with S-1 treatment. The 3-year OS rate was 80.1% in the adjuvant group and 70.1% in the surgery-only group [18]. Janunger *et al* performed a meta-analysis of 21 randomized studies and found a small survival benefit for the patients with postoperative adjuvant chemotherapy relative to patients who had undergone surgery alone (OR = 0.84, 95% CI 0.74 to 0.96) [19]. They found that the survival benefit was only apparent in Asian and not in Western patients. Therefore, they recommended adjuvant chemotherapy for Asian patients only. In the MAGIC trial, perioperative chemotherapy was found to benefit Western patients significantly [20]. These studies suggest that postoperative and perioperative chemotherapy may have survival benefits relative to surgery alone.

In our study, the 3-year and 5-year OS rates after postoperative sequential CRT were found to be 60% and 54%, respectively. This improved survival rate may

primarily be the result of the more extensive surgical methods (D2 lymph node resection). In the sequential CRT group, 76.7% of patients underwent D2 lymph node resection; whereas only 10% of the patients in the INT0116 trial underwent any kind of D2 dissection. Of these, 54% had a D0 dissection. In an analysis of variations in surgical treatment in an INT0116 trial, Hundahl *et al* pointed out that surgical undertreatment can undermine survival in gastric cancer patients [21]. Although the INT0116 study with its low D2 resection rate could not show whether postoperative CRT was better than surgery, other studies in Korea and Europe revealed that postoperative CRT could significantly reduce the rate of local recurrence and promote OS [22–23]. Another cause of this improved survival rate may have been the different races of the patients studied. Some Asian studies showed the OS rate of Asian patients with postoperative CRT to be higher than that of Western patients as mentioned above [19]. The main explanation may be that more cases of distal gastric cancer occur in Asian patients. Our study is a good example of this (68.5% distal gastric cancer). The use of new chemotherapeutic drugs, such as oxaliplatin, may have also contributed to the higher survival rate observed in sequential CRT treatment for advanced gastric cancer patients. Oxaliplatin was 10 times more quickly and tightly combined with DNA than cisplatin. Furthermore, the toxic effects of oxaliplatin were also lower than those of cisplatin. The toxicity of oxaliplatin in the gastrointestinal tract and kidneys has been shown to be significantly lower than that of cisplatin; therefore, oxaliplatin is more easily accepted by gastrointestinal cancer patients. Literature has shown chemotherapy with oxaliplatin and 5-FU for metastatic gastric cancer to be effective and highly tolerable [24–25]. A REAL-2 study showed that oxaliplatin could promote survival in gastric cancer [26]. In recent years, exploratory research has confirmed that docetaxel, oxaliplatin, and 5-FU along with concurrent CRT can improve the survival rate of locally advanced gastric cancer patients [27–28].

In this study, univariate analysis showed no statistically significant differences in survival. However, in multivariate analysis, the degree of tumor infiltration was affected in patients with gastric cancer. With the depth of tumor invasion increasing, from T1 to T4, the survival period of the patients decreased gradually. It will significantly shorten the survival time of patients when tumor penetrates serosa or invades serosa tissue.

Subgroup analysis revealed that the survival rate of patients with stage T3–T4 was lower than that of patients with stage T1–T2, and in multivariate analysis, the degree of tumor infiltration (T staging) affected OS and DFS of patients with gastric cancer. From stage T1 to T4, the survival rate decreased, especially for tissues of the serous or outer serous invaded by the tumor. This differs from the results of previous studies [9–11]. There was no difference in 3-year and 5-year survival rate by N stage or margins status (positive or negative). D2 lymph node dissection and CRT appeared to improve local-regional control and survival in N1–3 patients whose 3-year and 5-year survival rates were near the level of survival for early gastric cancer patients. Radiation might minimize the effects of stage on survival in locally advanced gastric cancer patients. However, the size of the sample examined in our study was small. These principles should be reevaluated through further study. After the 45 Gy radiotherapy, we boosted radiation to 50.4 Gy using small-field intensity-modulated radiation for positive margin patients. No difference in survival was observed between patients with positive and negative margins. Stiekema *et al* found that CRT significantly improved survival after a microscopically non-radical (R1) resection [29]. These results indicate that RT might be a suitable postoperative supplementary treatment.

Equally important, sequential CRT was designed to decrease the high levels of acute toxicity of normal concurrent CRT. It has been reported that the incidence rates for blood and gastrointestinal toxicities of postoperative CRT in gastric cancer were 10%–30% [30]. Changes in blood cells and gastrointestinal adverse effects were monitored closely in the sequential CRT group. The most common side effects were leucopenia, neutropenia, and gastrointestinal effects. Overall, sequential CRT treatment showed a decreased toxicity profile. The incidence of grade 3/4 leucopenia and granulopenia was below 10%. That of other types of toxicity was low (< 5%). Adverse effects were found to continue for 6 months to 1 year. Toxicity was tolerable after aggressive treatment, and no treatment-related deaths occurred. The 3D-CRT technique in our treatment resulted in equivalent CTV coverage with significantly decreased doses to the left kidney, liver, and gastrointestinal tract relative to the two anteroposterior fields in the INT0116 trial. No significant abnormal liver or kidney function was observed, despite the radiation doses administered to the liver and kidney during the current study. No delayed complications of the gastrointestinal tract, liver, or kidneys were observed after 3 years of follow up. We believe that this low toxicity was the most important reason why the curative effect of our trial was better than that of INT0116. Only 11.6% (17/146) of the patients were unable to complete the treatment due to gastrointestinal adverse effects.

Due to the lack of any postoperative chemotherapy-only group to use as a control, we could not ultimately determine whether the higher 3-year survival rate was the sole result of RT or whether RT and chemotherapy had equal effects. Although tumor staging did not turn out to be significant in our database, these results may

reflect that in a higher proportion of patients, poorly differentiated adenocarcinoma was in stage Ib–II; some patients may have had signet-ring cell carcinoma. Another reason for obtaining such unconventional results might be due to the fact that we had a 13.7% loss in the follow-up. If we assume all of them are alive, the survival rates could be substantially higher in patients with stage Ib–II disease. Therefore, the results of this study may not be representative of all gastric cancer cases in stage Ib–II but could demonstrate the fact that the majority of patients in stage III–IVa gastric cancer at our institution have similar survival to those in stage Ib–II after postoperative sequential chemotherapy and RT. We also acknowledge the necessity of enrolling more patients for further study. Meanwhile, it would be valuable to know whether intensity modulated radiation therapy (IMRT) is a better technique than 3D-CRT with respect to RT technology. The optimal regimen for postoperative CRT has not yet been established. Further studies on this topic must explore optimization of the chemotherapy regimen, define the role of RT, establish ways of integrating it into treatment schema (pre- vs. postoperative), and explore the effects of treatment timing (preoperative, postoperative, or both) [31–32]. Targeted therapies have recently made their way into the treatment of gastric cancer with the approval of trastuzumab for the treatment of metastatic gastric cancer with human epidermal growth factor receptor 2 positive [33]. Anti-angiogenics (bevacizumab) and anti-epidermal growth factor receptor agents (cetuximab) are also being studied in adjuvant settings.

In conclusion, for all patients with high-risk gastric cancer, especially pT3–T4 stage, the combination of postoperative local-regional radiation with systematic chemotherapy applied to patients in a sequential fashion is a feasible option. The effects of sequential CRT appear promising. The treatment was well tolerated with few grade 3 to 4 toxicities. Thus, further investigation into the role of postoperative sequential chemotherapy and RT in gastric cancer treatment is merited.

Conflicts of interest

The authors indicated no potential conflicts of interest.

Ethics statement

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (Approval ID: TJ-C20091211) and written informed consent was obtained from every participant. The study was conducted in compliance with the Declaration of Helsinki.

References

1. Chen W, Zheng R, Baade PD, *et al*. Cancer statistics in China, 2015. CA Cancer J Clin, 2016, 66: 115–132.
2. Chen W, Sun K, Zheng R, *et al*. Cancer incidence and mortality in China, 2014. Chin J Cancer Res, 2018, 30: 1–12.
3. Willett CG, Gunderson LL. Gastric cancer. In: Halperin EC, Perez CA, Brady LW, eds. Perez & Brady's principles and practice of radiation oncology. 5th ed. Lippincott Williams & Wilkins, 2012. 1318–1335.
4. Hartgrink HH, van de Velde CJ. Status of extended lymph node dissection: locoregional control is the only way to survive gastric cancer. J Surg Oncol, 2005, 90: 153–165.
5. Rahman R, Asombang AW, Ibdah JA. Characteristics of gastric cancer in Asia. World J Gastroenterol, 2014, 20: 4483–4490.
6. Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med, 2001, 345: 725–730.
7. Kozak KR, Moody JS. The survival impact of the intergroup 0116 trial on patients with gastric cancer. Int J Radiat Oncol Biol Phys, 2008, 72: 517–521.
8. Coburn NG, Govindarajan A, Law CH, *et al*. Stage-specific effect of adjuvant therapy following gastric cancer resection: a population-based analysis of 4041 patients. Ann Surg Oncol, 2008, 15: 500–507.
9. Smalley SR, Benedetti JK, Haller DG, *et al*. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol, 2012, 30: 2327–2333.
10. Kim S, Lim DH, Lee J, *et al*. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys, 2005, 63: 1279–1285.
11. Lee J, Lim DH, Kim S, *et al*. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol, 2012, 30: 268–273.
12. Fiorica F, Trovò M, Ottaiano A, *et al*. Can the addition of radiotherapy postoperatively increase clinical outcome of patients with gastric cancer? A systematic review of the literature and meta-analysis. Oncotarget, 2017, 9: 10734–10744.
13. Songun I, Putter H, Kranenbarg EM, *et al*. Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. Lancet Oncol, 2010,11: 439–449.
14. Degiuli M, Sasako M, Ponti A, *et al*. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. Br J Surg, 2010, 97: 643–649.
15. Yuan XL, Fu Q, Hu GQ, *et al*. Postoperative sequence chemoradiotherapy for advanced gastric cancer: an analysis of 36 cases. World Chin J Digestol (Chinese), 2007, 15: 3856–3859.
16. Hermans J, Bonenkamp JJ, Boon MC, *et al*. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol, 1993, 11: 1441–1447.
17. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer, 1999, 35: 1059–1064.
18. Sakuramoto S, Sasako M, Yamaguchi T, *et al*. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med, 2007, 357: 1810–1820.

19. Janunger KG, Hafström L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. Eur J Surg, 2002, 168: 597–608.
20. Cunningham D, Allum WH, Stenning SP, *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med, 2006, 355: 11–20.
21. Hundahl SA, Macdonald JS, Benedetti J, *et al*. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol, 2002, 9: 278–286.
22. Shim HJ, Kim KR, Hwang JE, *et al*. A phase II study of adjuvant S-1/cisplatin chemotherapy followed by S-1-based chemoradiotherapy for D2-resected gastric cancer. Cancer Chemother Pharmacol, 2016, 77: 605–612.
23. Mrena J, Mattila A, Böhm J, *et al*. Surgical care quality and oncologic outcome after D2 gastrectomy for gastric cancer. World J Gastroenterol, 2015, 21: 13294–13301.
24. Kim JY, Ryoo HM, Bae SH, *et al*. Multi-center randomized phase II study of weekly docetaxel versus weekly docetaxel-plus-oxaliplatin as a second-line chemotherapy for patients with advanced gastric cancer. Anticancer Res, 2015, 35: 3531–3536.
25. Liu Y, Feng Y, Gao Y, *et al*. Clinical benefits of combined chemotherapy with S-1, oxaliplatin, and docetaxel in advanced gastric cancer patients with palliative surgery. Onco Targets Ther, 2016, 9: 1269–1273.
26. Cunningham D, Okines AF, Ashley S. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med, 2010, 362: 858–859.
27. Xie J, Liang N, Qiao L, *et al*. Docetaxel, capecitabine and concurrent radiotherapy for gastric cancer patients with postoperative locoregional recurrence. Tumori, 2015, 101: 433–439.
28. Boda-Heggemann J, Weiss C, Schneider V, *et al*. Adjuvant IMRT/XELOX radiochemotherapy improves long-term overall- and disease-free survival in advanced gastric cancer. Strahlenther Onkol, 2013, 189: 417–423.
29. Stiekema J, Trip AK, Jansen EP, *et al*. The prognostic significance of an R1 resection in gastric cancer patients treated with adjuvant chemoradiotherapy. Ann Surg Oncol, 2014, 21: 1107–1114.
30. Chang JS, Koom WS, Lee Y, *et al*. Postoperative adjuvant chemoradiotherapy in D2-dissected gastric cancer: is radiotherapy necessary after D2-dissection? World J Gastroenterol, 2014, 20: 12900–12907.
31. Chai YX, Han Yu,Wang B, *et al*. Clinical study of docetaxel plus S-1 as neoadjuvant therapy for advanced gastric cancer. Oncol Transl Med, 2016, 2: 80–83.
32. Miceli R, Tomasello G, Bregni G, *et al*. Adjuvant chemotherapy for gastric cancer: current evidence and future challenges. World J Gastroenterol, 2014, 20: 4516–4525.
33. Bang YJ, Van Cutsem E, Feyereislova A, *et al*. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet, 2010, 376: 687–697.

DOI 10.1007/s10330-018-0261-1
Cite this article as: Fu Q, Yu SY, Hu GQ, *et al*. Postoperative sequential chemotherapy and radiotherapy for locally advanced gastric cancer. Oncol Transl Med, 2018, 4: 85–92.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0273-3

June 2018, Vol. 4, No. 3, P93–P100

ORIGINAL ARTICLE

Outcomes of palliative local treatment in metastatic colorectal cancer patients receiving chemotherapy plus bevacizumab

Ben Zhao, Lu Wang, Qianqian Yu, Guangyuan Hu, Hong Qiu, Mingsheng Zhang, Li Sun, Ping Peng, Xianglin Yuan (✉)

Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract

Objective The aim of this study was to assess the value of palliative local treatment of incurable metastatic lesions in colorectal cancer (CRC) patients receiving chemotherapy plus bevacizumab.

Methods Data of 105 patients with histologically confirmed synchronous or metachronous metastatic CRC who received bevacizumab treatment from January 1, 2011 to January 31, 2017 were retrospectively reviewed. Sixteen (15%) patients who were treated with bevacizumab for less than 4 cycles were excluded, and finally, 89 (85%) patients were enrolled. Among them, 33 (37%) patients who received palliative local treatment were categorized into the palliative local treatment group, and the remaining 56 (63%) patients were categorized into the chemotherapy plus bevacizumab group. The primary endpoint was overall survival (OS), which was calculated using Kaplan-Meier survival analyses. Factors possibly influencing survival were evaluated by univariate and multivariate analyses. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events, version 4.0. Grades 1–2 and 3–4 AEs of the two groups were compared and analyzed using the Fisher's exact test and χ^2 analysis.

Results The median follow-up period was 20.4 months, ranging from 1 to 60 months. The median OS in the palliative local treatment group was 36.3 months (95% CI, 33.5–39.2), and that in the chemotherapy plus bevacizumab group was 20.5 months (95% CI, 17.6–23.4). Both the univariate (HR 0.13, 95% CI, 0.05–0.30, $P < 0.001$) and multivariate (HR 0.16, 95% CI, 0.07–0.39, $P < 0.001$) analyses showed that the addition of palliative local treatment could prolong survival compared with chemotherapy plus bevacizumab alone. There were no significant differences in the rates of common chemotherapy- or bevacizumab-related AEs between the two groups.

Conclusion These findings suggest palliative local treatment is an effective and safe method for treating patients with incurable metastatic CRC receiving chemotherapy plus bevacizumab.

Key words: metastatic colorectal cancer; palliative local treatment; bevacizumab; chemotherapy; overall survival

Received: 19 April 2018
Revised: 16 May 2018
Accepted: 6 Junez 2018

Approximately 50%–60% of patients diagnosed with colorectal cancer (CRC) develop colorectal metastases, and > 65% of these patients have incurable metastatic disease [1–4]. Compared with patients undergoing complete resection of the metastatic and primary lesions, the outcome of those with incurable metastatic lesions is poorer. Fewer than 10% of the patients treated with standard chemotherapy are alive 5 years after treatment [2]. Even in the best case scenario of treatment with combined monoclonal antibodies, such as bevacizumab (a humanized monoclonal antibody that blocks the activity of vascular endothelial growth factor), long-term survival is modest, resulting in only about a 5-month improvement in overall survival (OS) [5–6]. The management of these patients with incurable metastases from metastatic CRC (mCRC) is a therapeutic challenge.

In recent years, a number of palliative local treatment methods have emerged in an attempt to treat incurable mCRC patients, including surgery, radiofrequency ablation, percutaneous microwave coagulation therapy

✉ Correspondence to: Xianglin Yuan. Email: xlyuan1020@163.com

(PMCT), transcatheter arterial chemoembolization (TACE), and radiation therapy (RT) [7–11]. Moreover, a recent retrospective study of 1,174 patients reported a survival benefit of palliative local treatment for patients with unresectable mCRC [12]. In this study, Yang *et al* found that the addition of palliative local treatment to chemotherapy was associated with a longer OS than chemotherapy alone (38.73 vs. 19.8 months, $P < 0.01$). The exploration of palliative local treatment reflects the fact that active local disease control plays an important role in the treatment of unresectable mCRC. However, more comprehensive data on the beneficial survival effect of this approach are lacking. No published studies have investigated the combined use of palliative local treatment, targeted drugs (bevacizumab), and chemotherapy in these patients, and the value of palliative local treatment combined with chemotherapy plus bevacizumab for incurable mCRC remains unclear.

The aim of the present study, therefore, was to assess the long-term effect of palliative local treatment of incurable metastatic lesions in mCRC patients receiving chemotherapy plus bevacizumab.

Materials and methods

Patient selection

This was a retrospective study conducted at the Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology. Here, we reviewed data of consecutive patients with histologically confirmed synchronous or metachronous mCRC treated with bevacizumab from January 1, 2011 to January 31, 2017. For all these patients, key eligibility criteria included: (1) treatment with bevacizumab for at least 4 cycles; (2) World Health Organization Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (3) adequate organ function according to the following laboratory values: absolute neutrophil count, > 1,500/μL; hemoglobin level, > 9.0 g/dL; platelet count, > 75,000/μL; bilirubin level, < 2.0 mg/dL; transaminase level, < 3 times the normal upper limit (5 times for patients with liver metastasis); and serum creatinine level, < 150 μmol/L; and (4) a life expectancy of > 3 months. Eligible patients were divided into two groups based on whether they received palliative local treatment. Palliative local treatment included surgery, PMCT, TACE and RT. Patients who underwent nontherapeutic exploratory laparotomy or emergency surgery for obstruction, hemorrhage and perforation, or biliary drainage were excluded from the palliative local treatment group. The remaining patients were categories into the chemotherapy plus bevacizumab group. The characteristics of the patients in both the groups are summarized in Table 1. The Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this retrospective study.

Systemic treatment regimen

Patients who had received standard palliative chemotherapy combined with bevacizumab were enrolled. The first- and second-line regimens included oxaliplatin- or irinotecan-containing chemotherapy. The third- and later-line therapies had no mandatory requirement. Bevacizumab was given at 5 mg/kg per 2 weeks or 7.5 mg/kg per 3 weeks respectively. One cycle was defined as 14 days or 21 days.

The dosage, delivery, and schedule of the main therapeutic regimens were administered according to the National Comprehensive Cancer Network guidelines (version 2, 2016). Bevacizumab was continued after first-line bevacizumab progression unless the patients refused treatment for cost, side effects or other reasons, in which case chemotherapy agents were changed from the first-line chemotherapy agents.

Principles of palliative local treatment

To evaluate whether cases with incurable metastases are suitable for palliative local treatment, careful discussion and supervision must be carried out by a multidisciplinary team (MDT) in our center. Before the administration of palliative local treatment, adequate assessment and communication should be undertaken among medical oncologists, radiologists, surgeons, and patients so that a suitable treatment strategy that optimizes related issues such as which lesions to treat and the timing of intervention can be developed. In general, the principles of palliative local treatment for cases with incurable metastatic lesions in our center are as follows: (1) to relieve symptoms, such as pain, hemorrhage, dysuresia, and bowel movement disorders, caused by intrapelvic tumors; (2) to prevent metastatic disease-related injury such as obstructive jaundice, pathological fractures of the bone and spinal cord paralysis; or (3) to control isolated new lesions or lesions that continue to enlarge when most of the remaining lesions are well-controlled (caused by tumor heterogeneity) during or after chemotherapy. In this study, patients were allowed to receive one or more types or multiple administrations of palliative local treatments. Written informed consent was required before palliative local treatment was administered.

Data information and statistical analysis

The clinicopathological parameters which we evaluated included age, sex, ECOG performance status, primary location (left or right side), grade of tumor differentiation, number of metastatic lesions, previous adjuvant chemotherapy (yes or no), KRAS status, pretreatment serum carcinoembryonic antigen (CEA)

levels (ng/mL), and survival period (months). The patient follow-up period ranged from 1 to 60 months, and the survival period was calculated from the date on which mCRC diagnosis was confirmed until the latest follow-up date. The detailed information of palliative local treatment among the 89 patients are summarized in Fig. 1, included the proportion and types of palliative local treatment administered. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events, version 4.0. Patient data and all patient follow-up information were collected into our electronic medical records database, including the latest follow-up or date of demise.

The primary endpoint was OS. Independent sample *t*-tests were used for statistical analysis of continuous variables, and the Fisher's exact test and χ^2 analysis were used, as appropriate, for categorical data. All factors possibly influencing survival were evaluated using univariate and subsequently, multivariate analyses. Survival curves were generated according to the Kaplan-Meier method, and the differences in patient survival periods were determined by employing the log-rank test. A P value < 0.05 was accepted as statistically significant. The Cox regression model and the Cox proportional hazards model were used for the analyses taking into account all variables simultaneously. All data were analyzed by the Statistical Package for the Social Sciences, version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Between January 1, 2011 and January 31, 2017, data of 105 consecutive mCRC patients who received bevacizumab treatment were retrospectively reviewed; 16 (15%) patients who were treated with bevacizumab for less than 4 cycles were excluded. Finally, 89 (85%) patients were enrolled. Among them, 33 (37%) received

Table 1 Characteristics of patients

Categorical Variable	Total (n = 89)		CT-B +local treatment (n = 33)		CT-B (n = 56)		P
	n	%	n	%	n	%	
Ages (years)							0.724
< 60	60	67.4	23	69.7	37	66.1	
≥ 60	29	33.6	10	30.3	19	33.9	
Sex							0.606
Male	49	55.1	17	51.5	32	57.1	
Female	40	44.9	16	48.5	24	42.9	
ECOG PS							0.936
0–1	67	75.3	25	75.8	42	75.0	
2	22	24.7	8	24.2	14	25.0	
Site of primary tumour							0.444
Left side	66	74.2	26	78.8	40	71.4	
Right side	23	25.8	7	21.2	16	28.6	
Tumor differentiation (grade)							0.142
Well/Moderate	50	56.2	23	69.7	27	48.2	
Poor	20	22.5	5	15.2	15	26.8	
Unknown	19	21.3	5	15.2	14	25.0	
Number of metastatic lesions							0.128
< 5	29	32.6	14	42.4	15	26.8	
≥ 5	60	67.4	19	57.6	41	73.2	
Previous adjuvant chemotherapy							0.106
Yes	31	34.8	15	45.5	16	28.6	
No	58	65.2	18	54.5	40	71.4	
KRAS status							0.270
Wild type	11	12.4	6	18.2	5	8.9	
Mutation type	29	32.6	8	24.2	21	37.5	
Unknown	49	55.1	19	57.6	30	53.6	
Pre-treatment CEA (ng/mL)							0.152
Normal (< 5 ng/mL)	32	36.0	15	45.5	17	30.4	
Abnormal (≥ 5 ng/mL)	57	64.0	18	54.5	39	69.6	

CT-B: chemotherapy plus bevacuzimab; ECOG PS: Eastern Cooperative Oncology Group performance status; CEA: carcinoembryonic antigen

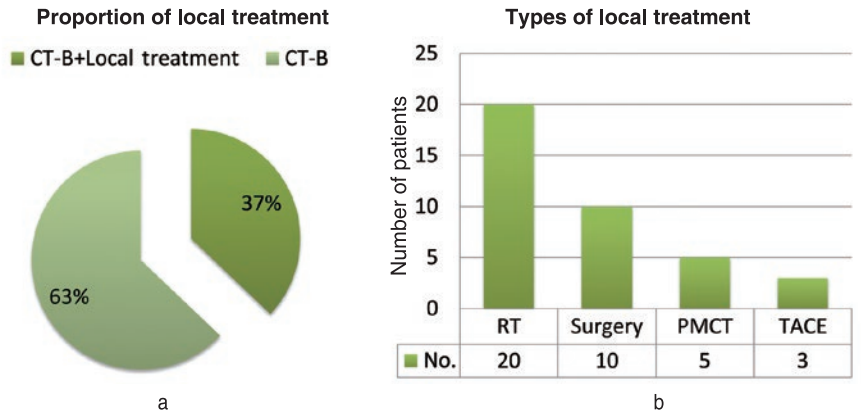


Fig. 1 Palliative local treatment in colorectal cancer patients with incurable metastatic lesions. (a) Pie chart of the proportion of palliative local treatment in colorectal cancer patients receiving combined treatment of chemotherapy and bevacizumab; (b) Histogram of the types of palliative local treatment in colorectal cancer patients with incurable metastatic lesions. RT: radiation therapy; PMCT: percutaneous microwave coagulation therapy; TACE: transcatheter arterial chemoembolization

palliative local treatment and were categorized into the palliative local treatment group, and the remaining 56 (63%) were categorized into the chemotherapy plus bevacizumab group (Fig. 2). The baseline characteristics were generally balanced between the two groups. There was no significant difference in relation to age, sex, ECOG performance status, primary location (left or right side), grade of tumor differentiation, number of metastatic lesions, previous adjuvant chemotherapy (yes or no), KRAS status, and pretreatment serum CEA levels (ng/mL) in the patients receiving palliative local treatment compared with those receiving chemotherapy plus bevacizumab. Additional details of the characteristics of all patients are summarized in Table 1.

The detailed information of palliative local treatment received by the 89 patients was well-summarized, as presented in Fig. 1. More than a third (37%) of the patients received palliative local treatment, and > 15% of them were treated with two different types of palliative local treatment. Of those administered palliative local treatment, 20 received RT for incurable metastatic lesions, 10 received surgery, 5 received PMCT, and 3 received TACE. The organs of local treatment were varied, and included the liver, lung, bone, ovary, lymph nodes of the retroperitoneal space and pelvic cavity, and metastatic nodules (Fig. 1).

Survival

The median follow-up period was 20.4 months, ranging from 1 to 60 months. Among the patients in the palliative local treatment group, 17 (52%) had died by the last follow-up and 16 (48%) were alive. In the chemotherapy plus bevacizumab treatment group, 29 (52%) patients had died by the last follow-up and 27 (48%) were alive. In the survival analysis of the 89 mCRC patients, the addition of palliative local treatment to chemotherapy and bevacizumab was associated with a significant increase in OS compared with chemotherapy plus bevacizumab alone (HR 0.13, $P < 0.001$, Fig. 3). The median OS with palliative local treatment and chemotherapy plus bevacizumab were 36.3 months (95% CI, 33.4–39.2) and 20.5 months (95% CI, 17.6–23.4), respectively.

Eight patient-, tumor-, and therapy-related characteristics that could potentially influence survival were identified in our study (Table 2). As more than half of the patients' KRAS status were unknown, we did not include it in further analyses. We found that two factors, including the number of metastatic lesions (HR 2.37, $P = 0.016$), and previous adjuvant chemotherapy (yes vs no, HR 2.32, $P = 0.014$) were significantly associated with outcome in a univariate analysis. A multivariate analysis adjusted for all 8 factors also indicated that the number of metastatic lesions (HR 2.55, $P = 0.015$), and previous adjuvant chemotherapy (yes vs no, HR 2.21, $P = 0.041$) were significantly associated with OS. Univariate analysis of the palliative local treatment for OS showed that the addition of palliative local treatment was associated with an increased OS (HR 0.13, 95% CI, 0.05–0.30, $P < 0.001$). This effect was virtually unchanged after adjustment for the number of metastatic lesions and previous adjuvant chemotherapy by multivariate analysis (HR 0.16, 95% CI, 0.07–0.39, $P < 0.001$), suggesting that the association between OS and palliative local treatment is independent of these factors (Tables 2 and 3). Furthermore, we performed multivariate analyses with adjustment for all the 8 factors listed in Table 2 and obtained similar results for OS (HR 0.16, 95% CI, 0.06–0.41, $P < 0.001$).

Safety

All patients in both groups experienced at least one AE. Among them, grade 1–2 and 3–4 AEs were compared between the two groups (Table 4). In both groups, the most frequently occurring AE was leukopenia, affecting 94% of the total patients in the palliative local treatment group and 92% of the total patients in the chemotherapy plus bevacizumab treatment group. Grade 3–4 AEs were not common in both groups. The most frequently occurring grade 3–4 AE was neutropenia, affecting 24% of the total

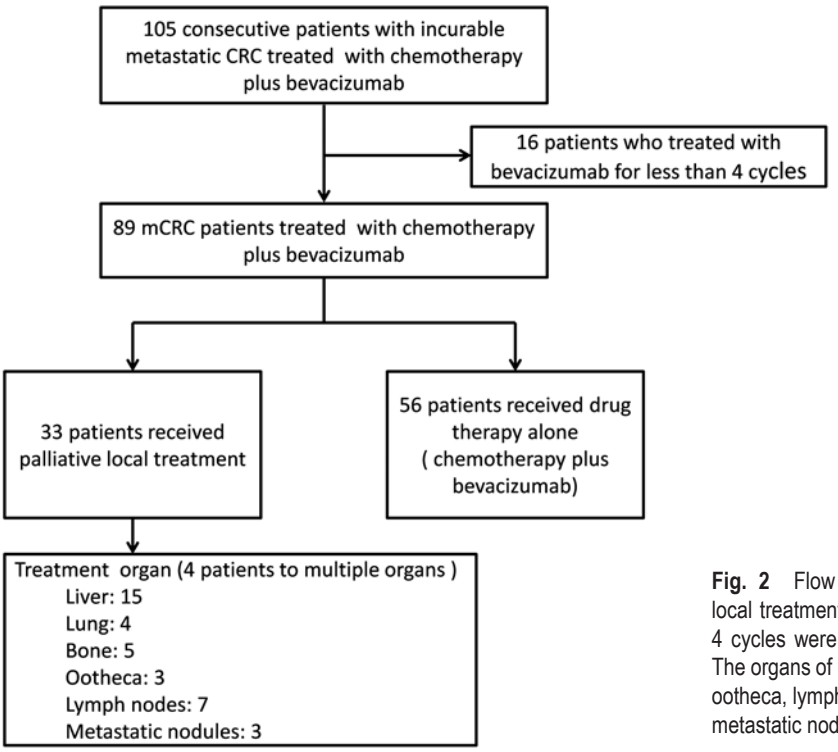


Fig. 2 Flow chart of patient inclusion and overview of palliative local treatment. 16 patients treated with bevacizumab for less than 4 cycles were excluded; a total of 89 patients were thus enrolled. The organs of local treatment were varied, including liver, lung, bone, ootheca, lymph nodes of retroperitoneal space and pelvic cavity, and metastatic nodules

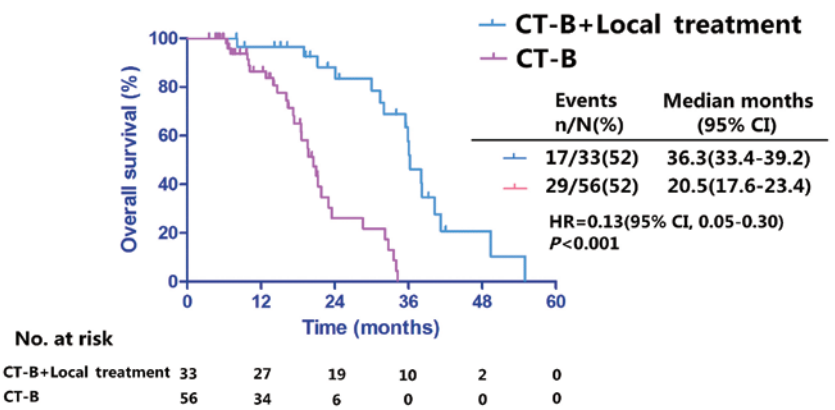


Fig. 3 Kaplan-Meier overall survival curves for patients who had received palliative local treatment combined with chemotherapy plus bevacuzimab or who had only received chemotherapy plus bevacuzimab. CT-B: chemotherapy plus bevacuzimab; HR: hazard ratio; CI: confidence interval

patients in the palliative local treatment group and 23% of the total patients in the chemotherapy plus bevacizumab group. There were no significant differences in the rates of common chemotherapy-related AEs between the two groups. It was worth noting that the bevacizumab-related AEs were also recorded and patients in the palliative local treatment group had similar rates of bevacizumab-related AEs as compared to those in the chemotherapy plus bevacizumab group. For example, the incident rates of grade 1 or 2 hypertension, proteinuria, and bleeding were 24%, 15%, and 42%, respectively, for the palliative local treatment group, and 21%, 18%, and 45%, respectively, for the chemotherapy plus bevacizumab group. The addition of palliative local treatment did not increase the rate of bevacizumab-induced AEs.

Discussion

Despite advances in chemotherapy, most patients with incurable mCRC succumb to the disease within 20 months of diagnosis [13]. In an effort to improve survival, new therapeutic approaches, such as targeted therapy and palliative local treatment, have gained much support in the last decade. Targeted therapies, such as bevacizumab, have been proven to be effective in combination with chemotherapy or as single agents for the treatment

Table 2 Univariate analysis and multivariate analysis of prognostic factors for overall survival using the Cox proportional hazards model, evaluated in all patients (n = 89)

Factors	Number of patients	Median OS (95% CI) (months)	Univariate analysis			multivariate analysis		
			HR	95% CI	*P*	HR	95% CI	*P*
Ages (years)								
< 60	60	30.0 (20.02–39.98)	1.000			1.000		
≥ 60	29	23.5 (11.16–35.84)	0.702	0.373–1.322	0.273	0.805	0.406–1.596	0.535
Sex								
Male	49	28.6 (18.05–39.15)	1.000			1.000		
Female	40	33.6 (17.49–49.71)	0.699	0.380–1.284	0.248	0.864	0.457–1.632	0.652
ECOG PS								
0–1	67	31.4 (20.18–42.62)	1.000			1.000		
2	22	23.0 (18.34–27.67)	1.415	0.683–2.928	0.350	0.978	0.418–2.289	0.959
Site of primary tumour								
Left side	66	30.0 (19.00–41.00)	1.000			1.000		
Right side	23	23.0 (6.44–39.56)	1.132	0.555–2.307	0.733	0.681	0.297–1.560	0.363
Tumor differentiation (grade)								
Well/Moderate	50	31.4 (24.87–37.93)	1.000			1.000		
Poor	20	19.0 (18.13–19.87)	1.825	0.896–3.718	0.097	1.536	0.676–3.485	0.305
Unknown	19	23.5 (18.78–28.22)	0.917	0.318–2.641	0.873	0.759	0.237–2.424	0.641
Number of metastatic lesions								
< 5	29	35.5 (32.84–38.16)	1.000			1.000		
≥ 5	60	23.0 (20.01–25.99)	2.365	1.172–4.771	0.016	2.549	1.197–5.426	0.015
Previous adjuvant chemotherapy								
Yes	31	35.5 (32.67–38.33)	1.000			1.000		
No	58	23.5 (12.66–34.34)	2.322	1.189–4.535	0.014	2.213	1.033–4.740	0.041
Pre-treatment CEA (ng/mL)								
Normal (< 5 ng/mL)	32	31.4 (20.19–42.61)	1.000			1.000		
Abnormal (≥ 5 ng/mL)	57	24.1 (12.26–35.94)	0.970	0.529–1.779	0.922	1.087	0.545–2.166	0.813

Multivariate analyses were adjusted for all factors listed in Table. OS: overall survival; NR: not reported; CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval

Table 3 Associations between palliative local treatment and overall survival based on univariate analysis and multivariate analysis

Palliative local treatment	Number of patients	Median OS (95% CI) (months)	univariate analysis			multivariate analysis		
			HR	95% CI	*P*	HR	95% CI	*P*
No (CT-B)	33	20.5 (17.63–23.37)	1.000			1.000		
Yes (CT-B + Local treatment)	56	36.3 (33.45–39.15)	0.127	0.054–0.302	< 0.001	0.161	0.066–0.394	< 0.001

Multivariate analyses in this table were adjusted for number of metastatic lesions and previous adjuvant chemotherapy. Similar results were obtained when multivariate analyses were adjusted for all the factors listed in Table 2 (data not shown). OS: overall survival; CT-B: chemotherapy plus bevacuzimab; HR: hazard ratio; CI: confidence interval

of mCRC, and they have been widely used in clinical practice [5, 14–16]. Recent studies have also confirmed that adding palliative local treatment improves the long-term outcome of incurable mCRC patients [11–12, 17]. Palliative local treatment has thus become another new treatment option for incurable mCRC.

These promising results prompted us to carry out the current study. To prove whether a more active treatment strategy could further improve the survival of incurable mCRC patients, we designed this retrospective study to identify the effectiveness of additional palliative local treatment in incurable mCRC patients who had received chemotherapy plus bevacizumab. As a result, we found that the addition of palliative local treatment to the standard treatment of chemotherapy plus bevacizumab could significantly improve survival for mCRC patients compared with those who had only received the standard treatment of chemotherapy plus bevacizumab. It should

Table 4 Adverse events relevant to treatment

Adverse events	CT-B +Local Treatment (*n* = 33)		CT-B (*n* = 56)		*P*
	Grade 1–2 *n* (%)	Grade 3–4 *n* (%)	Grade 1-2 *n* (%)	Grade 3–4 *n* (%)	
Leukopenia	25 (76)	6 (18)	40 (71)	12 (21)	0.906
Neutropenia	22 (67)	8 (24)	38 (68)	13 (23)	0.993
Anemia	19 (58)	2 (6)	31 (55)	1 (2)	0.507
Thrombocytopenia	14 (42)	1 (3)	25 (45)	1 (2)	0.918
Nausea	25 (76)	5 (15)	43 (77)	7 (13)	0.921
Vomiting	11 (33)	2 (6)	15 (27)	3 (5)	0.782
Diarrhoea	9 (27)	3 (9)	17 (30)	4 (7)	0.918
Fatigue	18 (55)	2 (6)	34 (61)	3 (5)	0.850
Thrombosis	0 (0)	0 (0)	0 (0)	1 (2)	0.440
Hypertension	8 (24)	3 (9)	12 (21)	7 (13)	0.865
Proteinuria	5 (15)	2 (6)	10 (18)	3 (5)	0.942
Bleeding	14 (42)	1 (3)	25 (45)	2 (4)	0.965
Any infection	12 (36)	2 (6)	19 (34)	1 (2)	0.519
Liver toxicity	8 (24)	1 (3)	18 (32)	1 (2)	0.697

Data are number (%) or p value. CT-B: chemotherapy plus bevacuzimab

be noted that the survival (median OS of 36.3 months) of the patients who had received combined treatment of chemotherapy, bevacizumab and palliative local treatment in our cancer center is one of the longest, as compared to historical published results of chemotherapy combined with bevacizumab [5, 18–20]. Of particular note, the patients included in our study all had highly advanced mCRC. Approximate 60% had more than 5 metastatic lesions. Moreover, the addition of palliative local treatment did not appear to exacerbate drug-induced grade 3 AEs, such as bleeding. In fact, we do not think the two new treatment options (targeted treatment and palliative local treatment) were independent of each other in improving survival of incurable mCRC patients. The addition of bevacizumab could significantly increase the tumor response rate, thus creating more opportunities for mCRC patients to accept more types and repeats of local treatment, further improving the survival of these patients. A combination of chemotherapy, targeted treatment and local treatment is important and effective in comprehensive treatment strategies and may be synergistic.

Our study had some limitations. First, this was a retrospective analysis of our experience. Second, the sample size of the study was small. Finally, there was a selection bias in patients receiving palliative local treatment, although we tried our best to reduce the bias by making treatment decisions using an MDT model. Further studies will be needed to address these issues.

In summary, the present study demonstrated that a survival benefit could be achieved with palliative local treatment of incurable metastatic lesions in mCRC patients who received chemotherapy and bevacizumab. However, considering the retrospective nature and small sample size of study, well-designed prospective clinical trials will be needed to validate these results.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Lee WS, Yun SH, Chun HK, *et al*. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. Int J Colorectal Dis, 2007, 22: 699–704.
2. Van Cutsem E, Nordlinger B, Adam R, *et al*. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer, 2006, 42: 2212–2221.
3. Yoo PS, Lopez-Soler RI, Longo WE, *et al*. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. Clin Colorectal Cancer, 2006, 6: 202–207.
4. Adam R, Delvart V, Pascal G, *et al*. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg, 2004, 240: 644–657.
5. Hurwitz H, Fehrenbacher L, Novotny W, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med, 2004, 350: 2335–2342.
6. Cunningham D, Humblet Y, Siena S, *et al*. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med, 2004, 351: 337–345.
7. Mineo TC, Ambrogi V, Tonini G, *et al*. Longterm results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. J Am Coll Surg, 2003, 197: 386–391.
8. Lorentzen T, Skjoldbye BO, Nolsoe CP. Microwave ablation of liver metastases guided by contrast-enhanced ultrasound: experience with 125 metastases in 39 patients. Ultraschall Med, 2011, 32: 492–496.
9. Zacharias AJ, Jayakrishnan TT, Rajeev R, *et al*. Comparative effectiveness of hepatic artery based therapies for unresectable colorectal liver metastases: a meta-analysis. PLoS One, 2015, 10: e0139940.
10. Hoyer M, Roed H, Traberg Hansen A, *et al*. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol, 2006, 45: 823–830.
11. Hsu CW, King TM, Chang MC, *et al*. Factors that influence survival in colorectal cancer with synchronous distant metastasis. J Chin Med Assoc, 2012, 75: 370–375.
12. Yang Q, Liao F, Huang Y, *et al*. Longterm effects of palliative local treatment of incurable metastatic lesions in colorectal cancer patients. Oncotarget, 2016, 7: 21034–21045.
13. Poston GJ, Figueras J, Giuliante F, *et al*. Urgent need for a new staging system in advanced colorectal cancer. J Clin Oncol, 2008, 26: 4828–4833.
14. Cao Y, Tan A, Gao F, *et al*. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. Int J Colorectal Dis, 2009, 24: 677–685.
15. Welch S, Spithoff K, Rumble RB, *et al*. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: a systematic review. Ann Oncol, 2010, 21: 1152–1162.
16. Simkens LH, van Tinteren H, May A, *et al*. Maintenance treatment

with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet, 2015, 385: 1843–1852.
17. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol, 2005, 23: 1358–1364.
18. Heinemann V, von Weikersthal LF, Decker T, *et al*. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol, 2014, 15: 1065–1075.
19. Schwartzberg LS, Rivera F, Karthaus M, *et al*. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol, 2014, 32: 2240–2247.
20. Venook AP, Niedzwiecki D, Lenz HJ, *et al*. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). J Clin Oncol, 2014, 32.

DOI 10.1007/s10330-018-0273-3
Cite this article as: Zhao B, Wang L, Yu QQ, *et al*. Outcomes of palliative local treatment in metastatic colorectal cancer patients receiving chemotherapy plus bevacizumab. Oncol Transl Med, 2018, 4: 93–100.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0254-4
2018, Vol. 4, No. 3, P101–P107

ORIGINAL ARTICLE

Risk factors for anastomotic leakage after low anterior resection without diversional stomas*

Xiaolong Chen[1], Libo Feng[1], Yu Liu[2], Xiaolong Wu[1], Jie Xu[1], Peng Chen[1], Zhonglin Zuo[1], Yi Liu[1], Qingwei Zou[1], Qing Liu[1], Dong Xia[1] (✉)

[1] Department of Gastrointestinal Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, China
[2] Department of Electrocardiograph, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, China

Abstract

Objective The most important complication after low anterior resection (LAR) for mid-low rectal cancer is symptomatic anastomotic leakage (AL). More than one-third of patients with rectal cancer who underwent LAR will have functional stomas during primary operation. The aim of this retrospective study was to evaluate the risk factors associated with clinical AL following LAR without diversional stomas.

Methods Between 2012 and 2017, information about 578 consecutive patients with rectal tumors less than 12 cm from the anal verge who underwent LAR without diversional stomas by the same surgical team was collected retrospectively. A standardized extraperitonealized anastomosis and pelvic drainage were conducted for all patients during primary operations, and the outcome of interest was clinical AL. The associations between AL and 14 patient-related and surgical variables were examined by both univariate chi-square test and multivariate logistic regression analysis.

Results The AL rate was 7.27% (42 of 578). Univariate and multivariate analyses showed that male sex (P = 0.018), mid-low rectal cancer (located 10 cm or less above the anal verge) (P = 0.041), presence of diabetes (odds ratio = 2.117), longer duration of operation (odds ratio = 1.890), and intraoperative contamination (odds ratio = 2.163) were risk factors of AL for LAR without diversional stoma and independently predictive of clinical AL. Nearly 83.3% (35 of 42) of leakage could be cured by persistent pelvic irrigation-suction-drainage without surgical intervention. Only 7 patients (16.7%) with severe complications, such as peritonitis, and fistula, required reoperation, and functional stoma was used as a salvage treatment.

Conclusion From the findings of this retrospective survey, we identified that mid-low rectal cancer and male sex were independent risk factors for developing clinical AL after LAR without diversional stomas, as well as longer duration of operation, presence of diabetes, and contamination of the operative field. Moreover, we deemed that LAR without diversional stomas for mid-low rectal cancers was safe, effective, and feasible. Extraperitonealized anastomosis and pelvic drainage obtained a relatively low rate of AL and avoided unnecessary functional stomas. Pelvic irrigation-suction-drainage was an effective procedure to resolve AL, and functional stoma was potentially used as a salvage modality for serious leakage.

Key words: anastomotic leakage (AL); low anterior resection (LAR); diversional stomas

Received: 2 February 2018
Revised: 15 April 2018
Accepted: 10 May 2018

With the emergence of advanced stapling devices and their increasing use to create low-level anastomosis, low anterior resection (LAR) with total mesorectal excision (TME) has become the preferred surgical option for mid-low rectal cancer. However, high anastomotic leakage (AL) rate and increased rate of proximal diversion have been reported in numerous surgical institutions. The rate of AL varies from 1% to 21% and is generally higher than 10% [1–6], depending on the anastomotic mode and inspection method. Clinical AL is a serious, sometimes disastrous, complication and a major cause of morbidity and mortality after anterior resection for rectal cancer. In particular, AL increases postoperative local recurrence and worsens long-term prognosis [7–8]. In

✉ Correspondence to: Dong Xia. Email: juliahhy@aliyun.com.
* Supported by a grant from the Education Department of Sichuan Province (No. 16ZA0197).

fact, the function of routine defunctioning stoma in the prevention of AL has been widely debated. A few clinical surveys demonstrated that 32.3% to 57% of patients with rectal cancer undergoing LAR would need protective defunctioning stomas during the primary operation [9–10]. Nevertheless, such prophylactic procedure is associated with a prominent reduction in the quality of life, including psychological health; in addition, 15% to 50% of initial temporary stomas would become permanent [11–12]. Moreover, diversional stoma itself extends the hospital stay and raises treatment costs, and the closure operation increases length of stay and costs [13]. With this associated controversy, defunctioning diversional stoma are considered cautiously.

Thus, a deep understanding of patients who are at a higher risk for developing AL in rectal cancer surgery is important for colorectal surgeons. To study the risk factors for clinical symptomatic AL following LAR without diversional stomas, we retrospectively collected data from 578 consecutive patients with mid-low rectal cancer in the Affiliated Hospital of Southwest Medical University, Luzhou, China, from January 2012 to December 2017. Moreover, the association between AL and perioperative variables was examined using univariate and multivariate analyses. It is worth mentioning that, during LAR without diversional stomas, extraperitonealized anastomoses, pelvic irrigation-suction-drainage, and/or functional colostomy, depending on the state, has been the standard treatment procedure for mid-low rectal cancer and AL after LAR in our hospital (The Affiliated Hospital, Southwest Medical University, Luzhou, China). Surely, we evaluated the efficacy and safety of this pelvic irrigation-suction-drainage modality to substitute the application of prophylactic functional stomas in this study.

Materials and methods

Patients and perioperative variables

From January 2012 to December 2017, 712 consecutive patients with tumors located less than 12 cm from the anal verge by preoperative colonoscopy or digital examination underwent rectum resection with curative intent for histologically proven adenocarcinoma in our department (Department of Gastrointestinal Surgery, The Affiliated Hospital, Southwest Medical University, Luzhou, China), including 578 LAR, 99 abdominoperineal resections, and 35 Hartmann's resections. LAR for mid-low rectal cancers was defined by the height of the anastomotic line below the level of peritoneal reflex, and the sphincter preservation rate was 81.2% (578 of 712). Patient characteristics, details of the surgical procedure, histopathologic parameters of tumors according to the criteria of the WHO and AJCC [14], and postoperative outcome and follow-up were documented prospectively, and all data were collected in a file and entered into our computer database. Due to the retrospective nature of this survey, approval by the ethics committee was not required.

In this study, a total of 578 patients undergoing LAR without primary functional stomas were included, and the outcome of interest was clinical AL. The seven patient-related variables were sex, age (< 65 years and ≥ 65 years), body mass index (BMI) in kg/m^2 (< 30 and ≥ 30), diabetes mellitus (defined as fasting plasma glucose level ≥ 7.0 mmol/L or with a glucose tolerance test, 2 h after the oral dose, a plasma glucose level ≥ 11.1 mmol/L), preoperative serum albumin level (< 3.0 g/dL and ≥ 3.0 g/dL), diameters of the tumor (≤ 3.0 cm and > 3.0 cm), and distance of the tumor from the anal verge (≤ 10 cm defined as mid-low rectal cancer). The seven surgical variables were blood transfusion, surgical procedures (open vs. laparoscopic techniques), duration of operation (≤ 210 min and > 210 min), intraoperative contamination (clean-contaminated vs. contaminated-dirty), resection of other organs simultaneously (such as invaded appendix, partial liver, or ovary for suspicious metastasis), tumor stage (quoted as a number I, II, III, and IV, derived from the TNM staging system of the AJCC), and resection type, curative or palliative (palliative resection defined as positive resection margin or intraoperatively diagnosed distal metastases that were not excised during this operation or local resection).

Surgical procedure and major management

All operations were performed by the same team of surgeons specializing in colorectal cancer surgery. We performed standardized TME procedure for mid-low rectal cancers as described by Heald [14]. Following the completion of anastomosis, the pelvic peritoneum was rebuilt to extraperitonealize the anastomosis by suturing the parietal peritoneum over the pelvic cavity to the sigmoid colon on the left and to the mesocolon on the right. Then, in the absence of leakage indication identified by transanal air insufflation, a double-catheterization cannula was cautiously placed just below the anastomotic line in the true pelvis and laterally diverted retroperitoneally passing through the left abdominal wall. Normally, if without any sign of suspected leakage, the drain tubes were completely extracted within 7 postoperative days. Irrigation-suction-drainage was conducted, if any sign of leakage is suspected.

The definition of AL in the present study was clinical: gas, pus, or fecal discharge from the drain, peritonitis, signs of rectovaginal fistula, pelvic abscess close to the anastomosis, or discharge of pus per rectum. Radiologically demonstrated leakage without clinical symptoms was excluded. In patients with AL, absolute diet, together

with empirical antibiotics, total parenteral nutrition support, and somatostatin infusion, was recommended. More importantly, a 50-mL syringe with normal saline was used to irrigate the input tube of the drainage slowly and deliberately and then suction the contents rapidly and effectively. Such kind of low-input irrigation was repeated 4 times per day, using 500 mL each time. When the quality of the outflow and inflow was almost equal and clear, the irrigation-suction was terminated, and normal drainage would resume with no further suction, and drainage was maintained through gravitational effect. Thereupon, we proceeded to observe the volumes of drainage until the flow ceased. Finally, the drainage cannula was retreated 1 to 2 cm gradually over 2 to 3 days and then completely extracted.

Relaparotomy with the intention of colostomy was performed as a salvage modality for patients with clinical AL, including (1) digital examination that demonstrated a major anastomotic ring defect more than one-third the circumference of the anastomosis; (2) signs and symptoms of infection diffused, persisted, or even worsened during conservative treatment; and (3) severe complications, such as peritonitis, rectovaginal fistula, or obstruction.

Statistical analysis

Clinical data were retrospectively collected from the institutional database. Statistical analysis was performed using SPSS software (IBM SPSS Statistics 21.0). The univariate relationship between each independent variable and clinical AL was evaluated using a logistic model for continuous variables and Pearson's chi-square test for categorical variables. Independent variables with a P-value ≤ 0.05 in the univariate analysis were included in the multivariate logistic regression model using a Wald statistic backward stepwise selection. A P-value < 0.05 was considered statistically significant.

Results

Of 578 consecutive patients who underwent LAR without diversional stomas included in the study, 58.8% were male (340 patients) and 41.2% were female (238 patients). Their median age was 63.5 years, ranging between 25 and 87 years. The mean anastomosis height from the dentate line was 4.8 cm (range, 0.5–10 cm). Clinical AL occurred in 42 patients, and the overall leakage rate was 7.27% (42 of 578). Three of 238 women (1.26%) developed rectovaginal fistula, which accounted for 3 of 10 leakages in women. All the leakages were noted on postoperative day 5.2 ± 4.5 except one, which developed 3 months after the primary operation. Seven leakages were reoperated during the initial hospital stay due to fecal peritonitis (42.9%, 3 of the 7 patients), rectovaginal fistula (42.9%, 3 of 7), and major anastomotic ring defect (14.2%, 1 of 7), and the reoperation rate was 16.7% (7 of 42). Relaparotomy and colostomy were performed as a salvage modality, and the postoperative recovery was uneventful. Six patients had successful closure of the diversional stomas within 5 to 6 months except one patient who refused to undergo one operation again due to insufficient financial support and advanced age. Accordingly, the other 35 leakages were treated by conservative method, and the median pelvic irrigation-suction-drainage time was 18 days (range, 7–36 days). In this series, no patients died of AL. The mean hospital stay was 12.04 days (SD, 6.29). Among the 42 patients with AL, the mean hospital stay was of 14.57 days (SD, 5.14), which was significantly greater than the hospital stay of patients without AL [(9.43 ± 7.44) days; P = 0.004].

Univariate analysis

Among all the 7 examined variables relating to patient characteristics, male sex and tumor location were the only factor that was statistically associated with development of clinical AL (Table 1). The AL rates of male and female sex were 9.41 and 4.20, respectively, with statistical significance (P = 0.18) by Pearson's chi-square test. The AL rate of mid-low rectal cancer was significantly higher than that of high rectal cancer. A higher frequency of AL was found in patients with lower rectal cancer (≤ 10 cm from the anal verge) (9.01% vs. 4.48%; P = 0.041) than that with higher rectal cancer. Table 2 shows the association

Table 1 Patients' characteristics and anastomotic leakage

Variables	No. of AL/total patients	Rate (%)	P value
Gender			0.018
Female	10/238	4.20	
Male	32/340	9.41	
Age (year)			0.753
< 65	19/275	6.90	
≥ 65	23/303	7.59	
Body mass index (kg/m^2)			0.755
< 30	8/121	6.61	
≥ 30	34/457	7.44	
Diabetes			0.063
Present	10/82	12.20	
Absent	32/496	6.45	
Preoperative albumin (g/dL)			0.995
< 3.0	5/69	7.25	
≥ 3.0	37/509	7.27	
Tumor size (cm)			0.911
≤ 3.0	18/243	7.41	
> 3.0	24/335	7.16	
Tumor location, from anal verge (cm)			0.041
≤ 10.0	32/355	9.01	
> 10.0	10/223	4.48	

Table 2 Surgical characteristics and anastomotic leakage

Variables	No. of AL/total patients	%	*P* value
Blood transfusion			0.236
Present	2/67	2.99	
Absent	40/511	7.83	
Procedure			0.155
Open	24/394	6.09	
Laparosopic	18/184	9.78	
Duration of operation (min)			0.086
≤ 210	19/192	9.90	
> 210	23/386	5.96	
Intraoperative contamination			0.069
Clean-contaminated	30/473	6.34	
Contaminated-dirty	12/105	11.43	
Other organs resection			0.986
Present	6/90	6.67	
Absent	36/488	7.38	
Resection			1.000
Curative	37/522	7.09	
Palliative	5/66	7.58	
Stages			0.208
I–II	0/26	0.00	
III–IV	42/552	7.61	

Table 3 Multivariate analysis

Variables	Odds ratio	95% CI	*P* value
Presence of diabetes	2.117	1.125–3.985	0.028
Duration of operation > 210 min	1.890	1.002–3.567	0.046
Contaminated or dirty operative field	2.163	1.083–4.320	0.026

between surgical characteristics and clinical AL. Presence of diabetes, duration of operation longer than 210 min, and contaminated or dirty wound were likely associated with a higher incidence of clinical leakages. Clinical leakages tended to develop in patients with the above three factors, which were evaluated in the multivariate analysis.

Multivariate analysis

After univariate analysis, significant variables were selected for multivariate analysis using a stepwise logistic regression model. Table 3 summarizes the significant results of multivariate analysis. Duration of operation longer than 210 min, contaminated or dirty wound, and presence of diabetes were independent predictive factors for clinical AL development.

Discussion

Since it was demonstrated in 1982, TME is now adopted as the standard therapy modality in low anterior resection for mid-low rectal cancer worldwide [15–17]. Despite the fact that TME is associated with lower local recurrence, higher sphincter preservation, and better survival, it is also associated with increasing risk of AL [18–20]. Although the advent of new instruments and novel techniques enabled the anastomosis for mid-low rectal cancer to be done more easily and quickly, AL after low anterior resection still remains as a challenging problem in the clinic, resulting in significant morbidity and mortality and poor prognosis [21]. As introduced in various studies, AL rates are inconsistent among different centers and institutions, ranging from 1% to 21% [4–6] but usually higher than 10%. An acceptable definition and grading system for AL for rectal cancer was proposed by the International Study Group of Rectal Cancer (ISGRC) in 2010 [22], which helps simplify grading of ALs, judge the severity, and make a proper therapeutic decision easily. According to this system, Grade A was defined as leakages that presented no clinical symptoms and signs that were only found through imaging study requiring no therapeutic intervention; Grade B was defined as leakages that led to clinical manifestations requiring active therapeutic intervention other than relaparotomy; Grade C was defined as leakages that had caused such serious consequences that reoperation was pressed for. In our present series, only Grades B and C leakages were included to facilitate valid comparison of the clinical results.

Although defunctioning stomas is widely used in LAR for mid-low rectal cancer in order to reduce the postoperative AL, whether patients would benefit from the protective stomas remains controversial. Several retrospective or non-randomized prospective investigations have demonstrated that absence of protective stomas is a risk factor for AL after LAR, considering that diverting the feces may construct a clean circumstance for anastomosis healing and decrease local infection; a leak may be avoided in the end [23–26]. However, the critics claim that it is not essential to have a defunctioning stoma for preventing a potential AL. In contrast, AL occurrence rate after LAR is not so high. The stoma itself may lead to many complications requiring proper treatment, even another operation. Finally, reoperation is inevitable for restoration of intestinal continuity, with increased pain and added costs, and it cannot be neglected that a several of temporary protective stomas become permanent [10, 27–29]. Hence, an increasing number of surgeons prefer the view that a functional stoma may mitigate the consequences as the complication generates but not reduce the incidence of AL following LAR for mid-low rectal cancer. Partly, as a result, some new techniques are attempted to prevent AL development, replacing diversional stomas, such as extraperitonealizing anastomoses by rebuilding the pelvis and placing pelvic drainage tubes.

In the present survey, extraperitonealized anastomoses

combined with double-catheterization cannulas were performed instead of colostomy or ileostomy in LAR for rectal cancer. The combination was routinely performed in all the patients undergoing LAR with mid-low rectal cancer, since it was carried out a few years in our department, because of its advantages, such as anastomotic extraperitonealization by closing the pelvic peritoneum, localizing the bleeding and inflammatory exudation, bowel contents, and pus, and draining out such contents by pelvic cannulas, which can experientially prevent AL, effectively treating breakdown anastomoses. It was again proved valid in this study, which demonstrated that the AL rate was 7.27% in accordance with the reported data of 1% to 21%.

Irrigation-suction was carried out when signs related to AL were perceived, such as variation in the drainage status with fecal or pus discharge, peritonitis, rectovesical fistula, rectovaginal fistula, or fever. Almost 83.3% of the patients suffering from AL were treated with this irrigation-suction-drainage strategy in our study. The remaining patients had to undergo relaparotomy to create a feces-diverting stoma. In other words, only 1.2% of all patients with mid-low rectal presenting a severe condition required diversional stomas as a salvage solution. This seems to suggest that primary ostomy is not essential, and current routine application of diversional stomas should be questioned [26, 30]. Moreover, the data also revealed that conjunction strategy can reduce the occurrence of AL and relaparotomy.

As reported, sex and the site of the tumor were considered risk factors for AL after LAR in this study. Male patients with mid-low rectal cancer seem to have a higher risk of AL, due to the small pelvis, which makes the operation more difficult for the surgeons, with either laparotomy or laparoscopy procedure [26, 30]. In our research, although there is a lower AL occurrence rate in female than male patients, another severe complication is frequently accompanying AL, namely, rectovaginal fistula, which brings about a terrible experience and longer treatment time. LAR has been accepted for treatment of mid-low rectal cancer, and obvious improvement in sphincter preservation was brought about, but lower anastomotic level was also confirmed as a negative impact for AL in the present study and other reported literature, along with frustrating anterior resection syndrome [31–33]; therefore, much effort would be needed to balance the two aspects in order to benefit more patients. Tumor localization determines anastomosis height; a lower site actually induces lower level of anastomotic ring. Tumor localization in the middle and lower third of the rectum, with subsequent lower anastomosis below the peritoneal reflection, has been widely accepted as a hazard for anastomotic defect [27, 34–35]. This may be caused by difficult mobilization of lower rectal tumors due to anatomical inaccessibility and reduced blood supply of the rectal stump and the pressure by pelvic hematoma or hydrops [36].

Few trials addressed these issues such as duration of surgery and contaminated surrounding of anastomoses. In the present study, operative time longer than 210 min presented as a risk factor for AL in the multivariate analysis, as well as a contaminated or dirty condition. A longer operation time for LAR was associated with a confined space, lower and larger tumor bulk, and harder resection and anastomosis, which were all identified as risk factors for anastomotic dehiscence [27, 34–35]. Contamination is the introduction of bacteria that cause infection and abscess development, enhancing anastomotic edema and delaying anastomotic healing, leading to development of an AL. Intraoperative contamination can be avoided by experienced professional colorectal experts; however, it is unavoidable when the preoperative intestinal preparation is poor or ileus is concomitant with the primary tumor.

Several reported research studies [37–39] illustrated that diabetes mellitus was significantly associated with AL. We obtained a similar result in the multivariate analysis in our study. Although some researchers [40] claimed that the presence of diabetes did not increase the AL rate after rectal resection, they emphasized that patients with diabetes with AL developed higher mortality compared with those without diabetes. Hence, presence of diabetes plays a significant role in the development of AL.

Based on the aforementioned results and discussion, we identified that mid-low rectal cancer and male sex were independent risk factors for developing clinical AL after LAR without diversional stomas, along with longer duration of operation, presence of diabetes, and contamination of the operative field. Moreover, we deemed that LAR without diversional stomas for mid-low rectal cancers was safe, effective, and feasible. Extraperitonealized anastomosis and pelvic drainage combined with irrigation and suction obtained a relatively low AL rate and avoided unnecessary functional stomas. Pelvic irrigation-suction-drainage was an effective procedure to resolve AL, and functional stoma was potentially used as a salvage modality for serious leakage.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Fielding LP, Stewart-Brown S, Blesovsky L, *et al*. Anastomotic integrity after operations for large-bowel cancer: a multicentre study. Br Med J, 1980, 281: 411–414.
2. Lee WS, Yun SH, Roh YN, *et al*. Risk factors and clinical outcome for anastomotic leakage after total mesorectal excision for rectal cancer. World J Surg, 2008, 32: 1124–1129.

3. Lin JK, Yueh TC, Chang SC, *et al*. The influence of fecal diversion and anastomotic leakage on survival after resection of rectal cancer. J Gastrointest Surg, 2011, 15: 2251–2261.
4. Akagi T, Inomata M, Etoh T, *et al*. Multivariate evaluation of the technical difficulties in performing laparoscopic anterior resection for rectal cancer. Surg Laparosc Endosc Percutan Tech, 2012, 22: 52–57.
5. Maggiori L, Bretagnol F, Lefevre JH, *et al*. Conservative management is associated with a decreased risk of definitive stoma after anastomotic leakage complicating sphincter-saving resection for rectal cancer. Colorectal Dis, 2011, 13: 632–637.
6. Rutegård M, Hemmingsson O, Matthiessen P, *et al*. High tie in anterior resection for rectal cancer confers no increased risk of anastomotic leakage. Br J Surg, 2012, 99: 127–132.
7. Mirnezami A, Mirnezami R, Chandrakumaran K, *et al*. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg, 2011, 253: 890–899.
8. Lin JK, Yueh TC, Chang SC, *et al*. The influence of fecal diversion and anastomotic leakage on survival after resection of rectal cancer. J Gastrointest Surg, 2011, 15: 2251–2261.
9. den Dulk M, Smit M, Peeters KC, *et al*. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. Lancet Oncol, 2007, 8: 297–303.
10. Gastinger I, Marusch F, Steinert R, *et al*. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg, 2005, 92: 1137–1142.
11. Torkington J, Khetan N, Jamison MH. Temporary decompression after colorectal surgery: randomized comparison of loop ileostomy and loop colostomy. Br J Surg, 1998, 85: 1452.
12. Kairaluoma M, Rissanen H, Kultti V, *et al*. Outcome of temporary stomas. A prospective study of temporary intestinal stomas constructed between 1989 and 1996. Dig Surg, 2002, 19: 45–51.
13. Koperna T. Cost-effectiveness of defunctioning stomas in low anterior resections for rectal cancer: a call for benchmarking. Arch Surg, 2003, 138: 1334–1339.
14. Hari DM, Leung AM, Lee JH, *et al*. AJCC Cancer Staging Manual 7th edition criteria for colon cancer: do the complex modifications improve prognostic assessment? J Am Coll Surg, 2013, 217: 181–190.
15. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? Br J Surg, 1982, 69: 613–616.
16. Leo E, Belli F, Andreola S, *et al*. Total rectal resection and complete mesorectum excision followed by coloendoanal anastomosis as the optimal treatment for low rectal cancer: the experience of the National Cancer Institute of Milano. Ann Surg Oncol, 2000, 7: 125–132.
17. Enker WE. Total mesorectal excision – the new golden standard of surgery for rectal cancer. Ann Med, 1997, 29: 127–133.
18. Scott NA, O'Flynn KJ, Carlson GL. Local recurrence following total mesorectal excision for rectal cancer. Br J Surg, 1996, 83: 1162–1163.
19. Law WL, Foo DC. Surgical results and oncologic outcomes for rectal cancer with tailored mesorectal excision over two decades. World J Surg, 2016, 40: 1500–1508.
20. de Jesus JP, Valadão M, de Castro Araujo RO, *et al*. The circumferential resection margins status: A comparison of robotic, laparoscopic and open total mesorectal excision for mid and low rectal cancer. Eur J Surg Oncol, 2016, 42: 808–812.
21. Yu QQ, Qiu H, Zhang MS, *et al*. Prognostic value of neutrophil-to-lymphocyte ratio in metastatic colorectal cancer. Oncol Transl Med, 2016, 2: 75–79.
22. Rahbari NN, Weitz J, Hohenberger W, *et al*. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery, 2010, 147: 339–351.
23. Koyama M, Murata A, Sakamoto Y, *et al*. Risk factors for anastomotic leakage after intersphincteric resection without a protective defunctioning stoma for lower rectal cancer. Ann Surg Oncol, 2016, 23 Suppl 2: S249–S256.
24. Gu WL, Wu SW. Meta-analysis of defunctioning stoma in low anterior resection with total mesorectal excision for rectal cancer: evidence based on thirteen studies. World J Surg Oncol, 2015, 13: 9.
25. Seo SI, Yu CS, Kim GS, *et al*. The role of diverting stoma after an ultra-low anterior resection for rectal cancer. Ann Coloproctol, 2013, 29: 66–71.
26. Snijders HS, van den Broek CB, Wouters MW, *et al*. An increasing use of defunctioning stomas after low anterior resection for rectal cancer. Is this the way to go? Eur J Surg Oncol, 2013, 39: 715–720.
27. Tortorelli AP, Alfieri S, Sanchez AM, *et al*. Anastomotic leakage after anterior resection for rectal cancer with mesorectal excision: incidence, risk factors, and management. Am Surg, 2015, 81: 41– 47.
28. Ihnát P, Guňková P, Peteja M, *et al*. Diverting ileostomy in laparoscopic rectal cancer surgery: high price of protection. Surg Endosc, 2016, 30: 4809–4816.
29. Snijders HS, van Leersum NJ, Henneman D, *et al*. Optimal treatment strategy in rectal cancer surgery: should we be cowboys or chickens? Ann Surg Oncol, 2015, 22: 3582–3589.
30. Nurkin S, Kakarla VR, Ruiz DE, *et al*. The role of faecal diversion in low rectal cancer: a review of 1791 patients having rectal resection with anastomosis for cancer, with and without a proximal stoma. Colorectal Dis, 2013, 15: e309–e316.
31. Kim CW, Baek SJ, Hur H, *et al*. Anastomotic leakage after low anterior resection for rectal cancer is different between minimally invasive surgery and open surgery. Ann Surg, 2016, 263: 130–137.
32. Jimenez-Gomez LM, Espin-Basany E, Marti-Gallostra M, *et al*. Low anterior resection syndrome: a survey of the members of the American Society of Colon and Rectal Surgeons (ASCRS), the Spanish Association of Surgeons (AEC), and the Spanish Society of Coloproctology (AECP). Int J Colorectal Dis, 2016, 31: 813–823.
33. Carrillo A, Enríquez-Navascués JM, Rodríguez A, *et al*. Incidence and characterization of the anterior resection syndrome through the use of the LARS scale (low anterior resection score). Cir Esp, 2016, 94: 137–143.
34. Jannasch O, Klinge T, Otto R, *et al*. Risk factors, short and long term outcome of anastomotic leaks in rectal cancer. Oncotarget, 2015, 6: 36884–36893.
35. Kim JS, Cho SY, Min BS, *et al*. Risk factors for anastomotic leakage after laparoscopic intracorporeal colorectal anastomosis with a double stapling technique. J Am Coll Surg, 2009, 209: 694–701.
36. Lee WS, Yun SH, Roh YN, *et al*. Risk factors and clinical outcome for anastomotic leakage after total mesorectal excision for rectal cancer. World J Surg, 2008, 32: 1124–1129.
37. Iancu C, Mocan LC, Todea-Iancu D, *et al*. Host-related predictive factors for anastomotic leakage following large bowel resections for colorectal cancer. J Gastrointestin Liver Dis, 2008, 17: 299–303.
38. Asari SA, Cho MS, Kim NK. Safe anastomosis in laparoscopic and robotic low anterior resection for rectal cancer: a narrative review and outcomes study from an expert tertiary center. Eur J Surg Oncol, 2015, 41: 175–185.
39. Wang L, Lu J, Liu Y, *et al*. A retrospective analysis of the safety and efficacy of apatinib in treating advanced metastatic colorectal cancer.

Oncol Transl Med, 2017, 3: 210–216.
40. Ziegler MA, Catto JA, Riggs TW, *et al*. Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: analysis from a statewide surgical quality collaborative. Arch Surg, 2012, 147: 600–605.

DOI 10.1007/s10330-018-0254-4
Cite this article as: Chen XL, Feng LB, Liu Y, *et al*. Risk factors for anastomotic leakage after low anterior resection without diversional stomas. Oncol Transl Med, 2018, 4: 101–107.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0272-2
June 2018, Vol. 4, No. 3, P108–P115

ORIGINAL ARTICLE

Comparison of computed tomography and magnetic resonance imaging for the detection of mandibular condylar osteochondroma*

Molun Shen[1, 3], Ling Zhu[2], Hongbo Yu[1], Lei Zhang[1], Xudong Wang[1](✉)

[1] Department of Oral and Craniomaxillofacial Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Stomatology, Shanghai 200011, China
[2] Department of Oral Radiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China
[3] Department of Oral and Maxillofacial Surgery, Hefei Stomatological Hospital, Hefei 230001, China

Abstract

Objective The purpose of this study was to compare computed tomography (CT) and magnetic resonance imaging (MRI) for the detection of mandibular condylar osteochondroma.

Methods Preoperative CT and MRI of 33 patients with unilateral condylar osteochondroma were reviewed. The morphology, location, continuity with the parent bone, cartilage cap, perichondrium of tumors, and changes in soft and hard tissues adjacent to the lesions were investigated by two reviewers. Data were analyzed using McNemar test. A P value < 0.05 was considered significant.

Results Among the 33 condylar osteochondromas, 11 were of the diffuse type, 10 were of the sessile type, and 12 were of the pedunculated type. Continuity with the cortex and marrow of the host condyle was observed on both CT and MRI. Both modalities had identical detection rates of surface reconstruction of the temporal bone joint, condylar dislocation, and pseudarthrosis formation. However, MRI showed significantly higher detection rates of the cartilage cap and perichondrium than CT (P < 0.05). Furthermore, MRI showed ipsilateral and contralateral temporo-mandibular joint (TMJ) disc displacement in 4 cases and 6 cases, respectively, and ipsilateral and contralateral TMJ effusion in 20 cases and 14 cases, respectively.

Conclusion CT can intuitively display the morphology and spatial location of condylar osteochondromas through three-dimensional reconstruction. MRI may be superior to CT in the detection of cartilage cap, perichondrium of the condylar osteochondroma, and changes in the TMJ and adjacent soft tissues.

Received: 14 April 2018
Revised: 5 May 2018
Accepted: 16 May 2018

Key words: mandibular condyle; osteochondroma; computed tomography (CT); magnetic resonance imaging (MRI)

Osteochondroma is the most-common benign tumor of long bones, but rarely occurs in the mandibular condyle [1]. The typical imaging features of osteochondroma are continuity with the cortex and marrow of the parent bones and a hyaline cartilage cap [2]. Computed tomography (CT) is the most-commonly used imaging modality for condylar osteochondroma: It clearly shows the characteristic continuity of the bone cortex and marrow of the tumor with the corresponding host condylar structures, but poorly demonstrates any uncalcified cartilage cap [3]. In comparison, magnetic resonance imaging (MRI) can directly display the cartilage cap covering the surface of osteochondromas due to its special cartilage signals and plays an important role in the diagnosis of the temporo-mandibular joint (TMJ) disorders [4].

In recent years, with the application of emerging technologies such as endoscopy and navigation, surgical skills for the treatment of condylar osteochondroma have greatly improved [5-7]. However, research progress on diagnostic imaging for this tumor has been slow. MRI studies of mandibular condylar osteochondromas are rarely reported in the literature, and no study has thus far

✉ Correspondence to: Xudong Wang. Email: xudongwang70@hotmail.com
* Supported by Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant (No. 20152225); and Shanghai Hospital Development Center Research Grant (No. SHDC12013103)

compared the efficacy of CT and MRI for its detection. Therefore, in this retrospective study, we analyzed the imaging data of 33 patients with condylar osteochondroma to compare the efficacy of CT and MRI for the detection of various characteristics of this rare disease.

Materials and Methods

Patients

From August 2009 to November 2016, 39 patients with unilateral mandibular condylar osteochondroma underwent surgical treatment at the Department of Oral and Craniomaxillofacial Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Six patients were excluded from our study because their preoperative CT or MR images were not available for review. Finally, 33 patients (6 men and 27 women) were included in this retrospective study. The enrolled patients had a mean age of 27.9 years (range, 17–56 years). The mandibular condylar osteochondroma was located in the left condyle in 14 cases and the right condyle in 19 cases. The final diagnosis of osteochondroma was confirmed by postoperative histopathological examination in all cases.

CT and MRI technique

Preoperative CT and MR images were obtained for all enrolled patients. Thin-cut (1.25 mm) spiral CT [LightSpeed 16 (GE, UK)] was performed with a matrix of 512 × 512 from the calvaria to the hyoid level in each patient. All patients underwent multiplanar reconstruction and volume rendering. The CT images were observed in both bone and soft-tissue windows.

MRI was performed using a 1.5-T unit [Signa Excite TwinSpeed (GE, USA)], with 6 × 8 cm special TMJ surface coils and spin-echo sequences. Proton density-weighted images (PDWI) were obtained in the oblique sagittal mouth-closing position [repetition time/echo time (TR/TE) = 1500.0–1820.0/20.2–20.8 ms, field-of-view (FOV)= 12 cm, slice thickness = 2 mm, matrix = 512 × 512] and the coronal mouth-closing position (TR/TE = 1840.0–2200.0/20.9–21.5 ms, FOV = 12 cm, slice thickness = 1.5 mm, matrix = 512 × 512). T2-weighted images (T2WI) were obtained in the oblique sagittal mouth-opening position (TR/TE = 3160.0–4000.0/81.0–83.2 ms, FOV = 12 cm, slice thickness = 2 mm, matrix = 512 × 512).

Image analysis

The preoperative CT and MR images of all patients were reviewed by a radiologist and a specialist in oral and maxillofacial surgery together. The two reviewers were blinded to the patients' clinical and histopathological information. Reviewer 1 (L.Z.) has > 15 years of oral radiology experience, and reviewer 2 (M.L.S.) has > 10 years of craniomaxillofacial surgery experience with 6 months of training in musculoskeletal radiology. The reviewers evaluated the CT images of each patient first and then the MR images. The morphology, location, continuity with the parent condyle, cartilage cap, and perichondrium of the tumors were analyzed. In addition, the adjacent soft and hard tissues such as the condyle, temporal articular surface, TMJ articular disc, articular cavity, and lateral pterygoid muscle were examined. The thicknesses of the cartilage caps on CT and MR images were measured using a standardized technique proposed by Bernard SA *et al* [8]. When the two reviewers' results were discordant, a third specialist performed a blinded, independent judgment.

Statistical analysis

All data were analyzed using the SPSS17.0 software package (IBM, USA). The McNemar test was used to analyze differences in detection rates of various pathological features and changes in adjacent tissues between CT and MRI. P values < 0.05 were considered statistically significant.

Results

Morphology and location of the condylar osteochondroma

Both CT and MRI clearly displayed the morphology and location of the condylar osteochondromas. However, the spatial position and morphology of the tumor was more innately portrayed by three-dimensional reconstruction of CT images than by MR images (Fig. 1C, Fig. 2C, Fig. 3C). Among the 33 condylar osteochondromas, 11 were of the diffuse type, 10 were of the sessile type, and 12 were of the pedunculated type (Table 1). The diffuse type showed a generally enlarged condyle without obvious boundaries between the tumor and the host condyle (Fig. 1). The sessile and pedunculated osteochondromas manifested exostoses connected with the surface of the condyles through wide bases (Fig. 2) and narrow stalks (Fig. 3), respectively. CT showed that the peripheral density of the tumor was higher than the density at the center, and the internal density was heterogeneous with scattered irregular calcification. MRI showed that the peripheral cortical bone of the tumor was rough with low-signal intensity on PDWI and T2WI. The internal bone marrow showed a moderate, high, or mixed signal on PDWI and T2WI.

In all patients with the diffuse type of osteochondroma, diffuse enlargement of the entire condyle was observed (11/11, 100.0%). Most of the sessile osteochondromas occurred at the anterior or anterior-medial surface of the condyle (5/10, 50.0%). The pedunculated osteochondromas were mostly located on the medial-

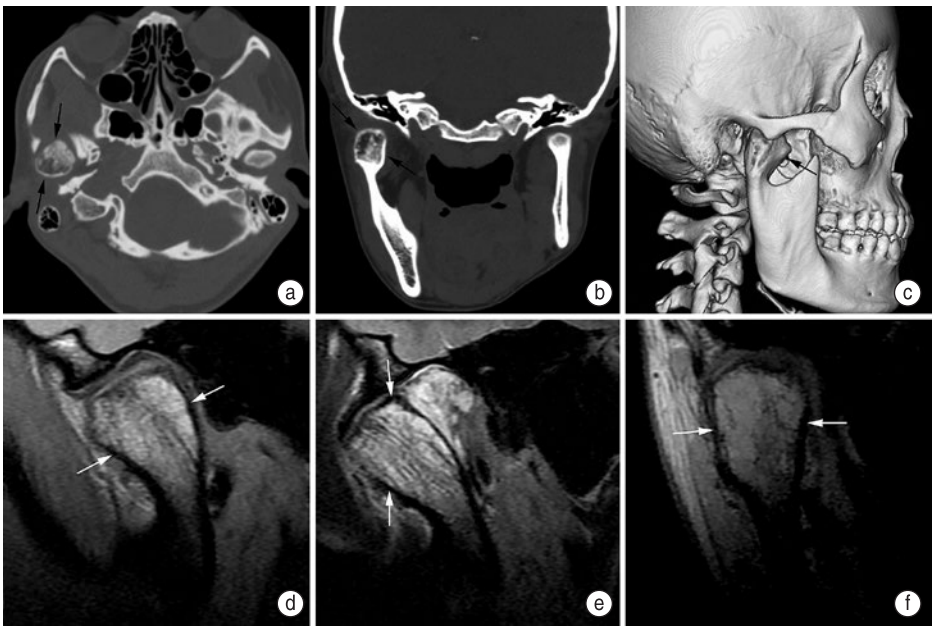


Fig. 1 Osteochondroma of the right condyle in a 27-year-old female patient (arrows). (a) Axial CT showed an enlarged right condyle with heterogeneous density and uneven surface; (b) Coronal CT presented a generally enlarged mass with a spherical shape and without obvious boundary between the lesion and the right condyle; (c) 3D-CT imaging showed a diffused bony outgrowth and significantly elongated ramus; (d) Oblique sagittal PDWI in closed mouth position showed a diffusely enlarged condyle with mixed signal intensity and uneven surface. The posterior belt of articular disc was located above the condyle; (e) Oblique sagittal T2WI in open mouth position showed a long T2 signal in the right articular upper cavity. The middle belt of articular disc was located at the top of the condyle; (f) Coronal PDWI in closed mouth position demonstrated a generally enlarged right condyle with moderate signal intensity.

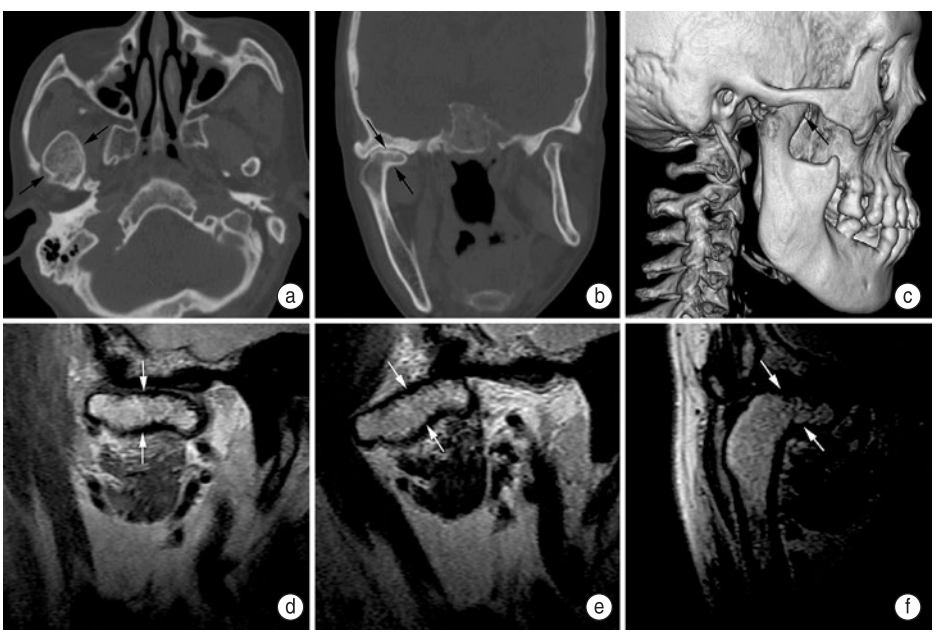


Fig. 2 Osteochondroma of the right condyle in a 56-year-old female patient (arrows). (a) Axial CT showed a bony exostosis arose from the medial area around the right condyle; (b) Coronal CT demonstrated a bony mass located on the medial-superior aspect of the right condyle with well defined border continuous with the parent condylar cortex and medulla; (b) 3D-CT imaging presented a sessile exostosis protruding from the medial-superior aspect of the right condyle. The affected condyle dislocated forward from the glenoid fossa; (d) Oblique sagittal PDWI in closed mouth position showed a high signal exostosis on the medial aspect of the right condyle; (e) Oblique sagittal T2WI in open mouth position showed a high signal exostosis with low signal rim; (f) Coronal PDWI in closed mouth position demonstrated a sessile tumor was located on the medial-superior aspect of the right condyle and was continuous with the underlying condylar cortex and marrow.

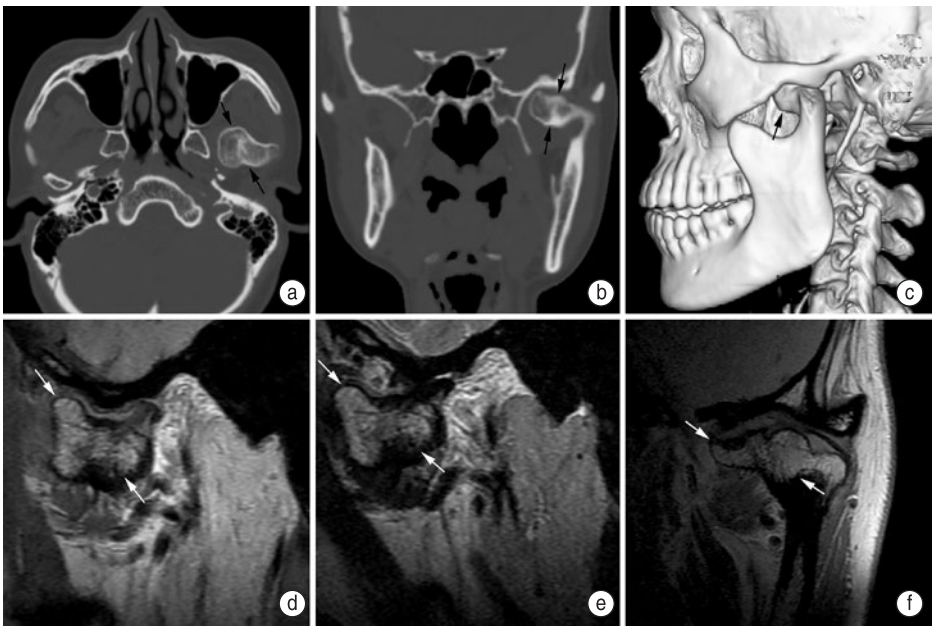


Fig. 3 Osteochondroma of the left condyle in a 32-year-old female patient (arrows). (a) Axial CT showed a bony exostosis arose from the medial area around the left condyle; (b) Coronal CT demonstrated a pedunculated mass located on the medial-superior aspect of the left condyle; (c) 3D-CT imaging showed the left condyle dislocated from the glenoid fossa; (d) Oblique sagittal PDWI in closed mouth position showed a bony tumor on the left condylar anterior-superior edge with mixed signal intensity and the posterior belt of articular disc was located above the condyle; (e) Oblique sagittal T2WI in open mouth position showed there was no change of the relationship of the disc with the condyle when opening mouth with long T2 signal in the articular cavity; (f) Coronal PDWI in closed mouth position demonstrated a pedunculated tumor was located on the medial-superior aspect of the left condyle and was continuous with the underlying condylar cortex and marrow.

superior surface of the condyle (7/12, 58.3%) (Table 1). The condylar osteochondromas presented in varying shapes including spherical (11 cases), hemispherical (4 cases), triangular (4 cases), rectangular (4 cases), beak-like (3 cases), pseudopodia (2 cases), thorn (2 cases), oval (1 case), lip-like (1 case), and cauliflower (1 case).

Table 1 Presenting tumor location surrounding the condyle in 33 cases of condylar osteochondroma

Tumor location	Tumor type (*n*, %)		
	Pedunculated	Sessile	Diffuse
Generally enlarged	0	0	11 (100.0%)
Top	0	1 (10.0%)	0
Posterior-superior	1 (8.3%)	0	0
Simple medial	1 (8.3%)	0	0
Medial-superior	7 (58.3%)	1 (10.0%)	0
Anterior	0	3 (30.0%)	0
Anterior-medial	1 (8.3%)	2 (20.0%)	0
Anterior-superior	1 (8.3%)	1 (10.0%)	0
Lateral-anterior	1 (8.3%)	1 (10.0%)	0
Lateral-posterior	0	1 (10.0%)	0
Total	12 (100.0%)	10 (100.0%)	11 (100.0%)

Detection of various characteristics of condylar osteochondroma on CT and MRI

In all cases, CT and MRI showed the characteristic continuity of the bone cortex and marrow of the osteochondroma with the corresponding host condylar structures (Table 2). The detection rates of the cartilage cap on CT (12 cases, 36.4%) was significantly lower than that on MRI (21 cases, 63.6%) ($P < 0.05$, Table 2). In 12 cases, the thickness of the cartilage caps measured on CT ranged from 2.7 mm to 8.8 mm, with an average of 5.4 mm. The density of the cartilage cap was slightly higher than that of the masticatory muscles. On MRI, the cartilage cap thicknesses in 21 cases ranged from 3.0 mm to 8.5 mm, with an average of 4.6 mm. The cartilage caps showed high-signal or mixed-signal intensity on PDWI and T2WI. The shapes of the cartilage caps were cauliflower-like or irregular and massive.

The detection rates of the perichondrium of the osteochondromas were significantly lower by CT (2 cases, 6.1%) than by MRI (15 cases, 45.5%) ($P < 0.05$, Table 2). On PDWI and T2WI, the perichondrium showed a thin layer of fibrous rings with low-signal intensity around the surface of the cartilage cap. On CT, the density of the perichondrium was slightly lower than that of the masticatory muscles.

Table 2 Comparison of CT and MRI for the detection of various characteristics in 33 cases of condylar osteochondroma

Characteristics	CT		MRI		*P*
	n	%	*n*	%	
Continuity with the parent condyle	33	100.0	33	100.0	/
Cartilage cap	12	36.4	21	63.6	0.004
Perichondrium	2	6.1	15	45.5	0.001
Compressive reconstruction of the temporal bone articular surface	8	24.2	8	24.2	/
Condylar dislocation	10	30.3	10	30.3	/
Pseudojoint	12	36.4	12	36.4	/
Fatty degeneration of the affected lateral pterygoid muscle	3	9.1	8	24.2	0.063
Disc displacement at the affected side	/	/	4	12.1	/
Disc displacement at the contralateral side	/	/	6	18.2	/
Joint effusion at the affected side	/	/	20	60.6	/
Joint effusion at the contralateral side	/	/	14	42.4	/

Detection of the changes in adjacent tissues on CT versus MRI

The results of CT and MRI were consistent with regard to the detection rates of the changes of the affected temporal articular surface, condylar dislocation, and pseudojoint (Table 2). The temporal articular surfaces were flattened due to compression by the tumors in 8 cases (24.2%). The affected condyles were dislocated from the glenoid fossa in 10 cases (30.3%; 5 cases of downward dislocations, 4 cases of forward dislocations, 1 case of lateral displacement). In 10 cases of condylar dislocations, all the osteochondromas occurred at the superior areas around the affected condyle, such as the medial-superior aspect (7 cases, Fig. 2 and 3), the anterior-superior aspect (2 cases), and the top (1 case). In 12 cases (36.4%), the tumor formed a pseudojoint under the anterior joint eminence or middle-skull base.

The detection rates of the affected lateral pterygoid muscle atrophy and fatty degeneration by CT and MRI were 9.1% (3 cases) and 24.2% (8 cases), respectively, with no statistically significant difference ($P > 0.05$, Table 2). CT showed that the affected lateral pterygoid muscle density decreased heterogeneously. MRI showed that the affected lateral pterygoid muscle contained dispersed streaky or patchy high-signal intensities on PDWI and T2WI.

Changes in the affected and contralateral TMJ

CT did not show TMJ articular disc and joint effusion. However, MRI clearly showed disc displacement in the TMJ (Table 2). Four patients (12.1%) had a disc displacement in the affected side (2 cases of irreversible anterior displacement, 1 case of reversible anterior displacement, and 1 case of medial displacement). Six cases (18.2%) had a disc displacement in the contralateral TMJ (3 cases of irreversible anterior disc displacement, 1 case of reversible anterior displacement, 1 case of reversible medial-anterior displacement, and 1 case of irreversible lateral-anterior displacement). Joint effusion was clearly observed on MR images (Fig. 1, Fig. 3, Table 2). Twenty cases (60.6%) of the affected TMJ and 14 cases (42.4%) of the contralateral TMJ had joint effusions presenting as long T2 signals.

Discussion

Condylar osteochondroma usually grows slowly and presents with similar signs and symptoms as TMJ disorders; therefore, it may be misdiagnosed in the early stages [1, 9]. CT is the most-commonly used imaging modality that yields clear bone-tissue images. Through three-dimensional reconstruction of CT images, the position and morphology of the tumor can be innately observed, and the connection between the tumor and the mandibular condyle and glenoid fossa can be clearly visualized [10]. MRI can clearly illustrate the continuity of the osteochondroma and the parent bone as well as the connection between the tumor and its surrounding soft and hard tissues from the multi-planner views. The existence and thickness of the cartilage cap of the tumor can be directly observed by the special cartilage signal on MR images [2, 4]. However, the MRI findings of condylar osteochondroma have thus far only been mentioned in a few case reports, and the literature lacks studies with a large sample size[11–12].

Osteochondromas usually represent pedunculated or sessile exophytic bony protrusions attached to the metaphyseal region of long bones, which are also known as osteocartilagenous exostosis. The sessile and pedunculated tumors are connected with the host bones

through wide bases and narrow stalks, respectively [2]. However, in addition to exogenous excrescence, condylar osteochondromas could manifest with a diffuse growth pattern involving the entire condyle [10–11, 13–14]. In our study, 11 of the 33 tumors were of the diffuse type, with the overall shape of the affected condylar increasing as compared to the contralateral side. Due to the absence of an obvious boundary between the tumor and the host condyle, the diffuse osteochondroma was difficult to differentiate from condylar hyperplasia.

Stress in areas of the tendinous insertion, where the cells with cartilaginous potential accumulate focally, is a possible factor for osteochondroma formation [15]. This possibility is supported by some early studies that showed that most condylar osteochondromas occurred at the anterior-medial surface of the condyle at the attachment of the pterygoid muscle [13]. However, in recent years, studies found that the lesions could be located at different sites encircling the condyle, such as the lateral, anterior-lateral, anterior, superior, and posterior aspect of the condyle [10, 14], which questions the possibility of stress as a factor for osteochondroma formation. In addition, this study showed that the condylar osteochondroma could grow around different parts of the condyle. Although the condylar medial surfaces (including the simple medial, medial-superior, anterior-medial aspects) were the main sites of tumor growth, these aspects constituted only 36.4% of all cases (12/33; Table 1). The tumor also occurred in the top, posterior-superior, anterior, anterior-superior, lateral-anterior, and lateral-posterior surface of the condyle. Zhang *et al*. argued that osteochondromas might occur at any site of the condyle as long as continuous local stimulation persisted [14], which is in line with our findings. Both CT and MRI have multiple-planar imaging capabilities. As such, both modalities can present the growth position and morphology of osteochondroma from several different perspectives. However, CT images can be reconstructed to obtain a three-dimensional digital model to display the condylar tumor more innately. Moreover, computer-assisted surgical simulation and navigation-guided resection of the condylar osteochondroma could be further performed with reference to the three-dimensional digital model of CT images [5–7]. This advantage of CT imaging was unmatched by MRI. In our study, the condylar osteochondromas exhibited varying shapes such as spherical, beak-shaped, hemispherical, pseudopodia, triangular, rectangular, thorn-shaped, oval, lip-like, and cauliflower-like. The adjacent anatomical structures such as the articular eminence, glenoid fossa, articular capsule, maxillary tubercle, and external auditory canal may play a shaping effect on condylar osteochondromas by limiting tumor extension [10, 14].

The continuity of the cortex and medulla of the tumor with the corresponding structures of the parent bone is considered a diagnostic characteristic for osteochondromas [16]. Plain film usually shows this characteristic appearance in lesions of the long bones with standard radiographic projections. However, for osteochondromas occurring in complex areas of anatomy, the continuity may not be apparent on plain radiography. However, CT and MRI with multiple-planar imaging capability often allow optical depiction of the pathognomonic continuity of the lesion and parent bone [2]. This study showed that both CT and MRI could reveal the cortical and marrow continuity of the lesion and the host condyle.

Another important feature of osteochondromas is the hyaline cartilage cap covering the tumor surface. The thickness of the cartilage cap is important to identify malignant transformation of the tumor. CT can show calcified cartilage caps, but it is difficult to identify uncalcified cartilage caps with density similar to the adjacent soft tissue on CT images [2, 17]. As such, MRI is the optimal imaging modality to illustrate the hyaline cartilage cap of osteochondromas. The large water content of the uncalcified cartilage cap provides a very-high signal intensity on T2WI. The cartilage cap has a low-signal intensity in the calcified regions on all pulse sequences of MRI and eventually turns into a yellow bone-marrow signal with the process of ossification [4, 17]. These features allow MRI to differentiate the cartilage cap from the surrounding soft tissues and accurately measure the thickness of the cartilage cap. The current study showed that the detection rate of the cartilage cap with MRI (63.6%) was significantly higher than that with CT (36.4%). The thickness of cartilage cap is related to the degree of skeletal maturity. The thickness of the cartilage cap is generally 1–3 cm in young patients, but only a few millimeters or even completely absent in adults. When the thickness of the cartilage cap is > 2 cm in skeletally mature adults, a malignant transformation into chondrosarcoma is highly suspected [8, 17]. In our study, none of the patients had a cartilage cap thickness of ≥ 2 cm or malignant transformation. When the cartilage cap covering the tumor surface grew thinner or was even missing due to ossification, the condylar osteochondroma could be easily misdiagnosed as condylar hyperplasia.

Histologically, osteochondromas often manifest as a thin layer of fibrous annular perichondrium on the surface of the cartilage cap [18]. The perichondrium has a similar density as the surrounding skeletal muscles, which is difficult to detect on CT. On MR images, the perichondrium manifests as a thin layer of low-signal area surrounding the surface of the cartilage cap. If the underlying cartilage cap shows low-signal intensity due to complete calcification, the presence of the perichondrium will be difficult to detect on MR images [2, 17, 19]. This study showed that MRI had a significantly higher detection rate of the perichondium (45.5%) than CT (6.1%).

Although osteochondroma is benign, it may cause pressure erosion of the adjacent bone tissues due to progressive expansion [17]. The condylar osteochondroma, especially protruding superiorly or expanding extensively, often causes compressive reconstruction of the temporal bone joint surface [10] and even invades the skull base [16]. Eight of the 33 cases in our study showed flattened temporal bone articular surfaces as compared to the opposing side due to the compression of the tumor body. With the condylar osteochondroma gradually growing, especially when extending upward, pseudojoints could be slowly formed between the anterior joint eminence or the middle cranial base and the tumor; further, the affected condyles could dislocate from the glenoid fossa [10]. In our study, there were 12 cases (36.4%) of pseudoarthrosis and 10 cases (30.3%) of condylar dislocation. Among these cases, all tumors were located at the top or in the superior aspect of the condyle.

Osteochondroma may cause alterations in adjacent soft-tissue structures. Buoncristiani *et al*. reported that MRI showed fatty degeneration of the ipsilateral lateral pterygoid muscle in a case of osteochondroma originating from the glenoid fossa [20]. Furthermore, Avinash *et al*. reported that CT images in the soft-tissue window demonstrated fatty infiltration and muscular atrophy of the ipislateral masticator muscle in a case of condylar osteochondroma [3]. Due to excellent soft-tissue resolution, MRI has more advantages over CT with regard to revealing the soft-tissue changes around the tumor. Accordingly, a previous study reported MRI as a reliable method for assessing the presence of muscular atrophy with fatty degeneration [17]. Similarly, our study showed that MRI had a higher detection rate of the affected lateral pterygoid muscle atrophy with fatty infiltration than CT, although the difference was not statistically significant. Muscular atrophy with fatty degeneration might be a functional response of the masticatory muscles to the aberrant mandibular position caused by condylar osteochondroma [20].

The literature includes a few studies on the structural changes of the TMJ in patients with condylar osteochondroma. However, only a few studies on the radiographic presentation of condylar osteochondroma on plain films and CT images analyzed the changes in bone tissues such as reconstruction of the temporal bone joint surface and condylar dislocation [10]. Thus far, there is no report on articular disc displacement and joint effusion. CT did not clearly show the articular disc and joint effusion. However, MRI was considered a gold standard for evaluating the shape and position of the TMJ disc. The display rate of the articular disc by MRI was 100%, and the joint effusion state could also be observed by MRI [21]. Condylar osteochondroma can cause a change in the connection between the articular disc and the condyle. In this study, MRI showed that 4 patients had a disc displacement in the affected side. Of note, the tumor could also cause an articular disc displacement at the contralateral TMJ, and contralateral disc displacement was more common and more complex than disc displacement on the affected side. In this group, 6 patients had articular disc displacement at the contralateral side, including various situations such as reversible anterior displacement, irreversible anterior displacement, reversible medial-anterior displacement, and irreversible lateral-anterior displacement. In addition to the 20 cases of ipsilateral joint effusion, MRI showed that 14 cases of contralateral TMJ had joint effusion. Condylar osteochondroma often leads to a habit of unilateral mastication due to cross-bite on the contralateral side and open bite on the affected side [10, 22]. This might cause changes in the contralateral TMJ structures.

Conclusions

Both CT and MRI clearly demonstrate the characteristic continuity of condylar osteochondroma with the underlying native condylar cortex and medulla as well as changes in the adjacent hard tissue. Three-dimensional reconstruction of CT images could display the tumor's spatial position and morphology more innately than MRI. However, MRI may be superior to CT in revealing the cartilage cap and perichondrium as well as the changes in the TMJ and adjacent soft tissues.

Conflict of interest

The authors indicated no potential conflicts of interest.

References

1. Wilson GJ, Gardner A, Downie J, *et al*. Progressive facial asymmetry resulting from condylar osteochondroma – A case report detailing the resection, subsequent orthognathic intervention and custom joint replacement. J Oral Biol Craniofac Res, 2015, 5: 102–105.
2. Murphey MD, Choi JJ, Kransdorf MJ, *et al*. Imaging of osteochondroma: variants and complications with radiologic-pathologic correlation. Radiographics, 2000, 20: 1407–1434.
3. Avinash KR, Rajagopal KV, Ramakrishnaiah RH, *et al*. Computed tomographic features of mandibular osteochondroma. Dentomaxillofac Radiol, 2007, 36: 434–436.
4. Kim HK, Horn P, Dardzinski BJ, *et al*. T2 Relaxation Time Mapping of the Cartilage Cap of Osteochondromas. Korean J Radiol, 2016, 17: 159–165.
5. Yu HB, Sun H, Li B, *et al*. Endoscope-assisted conservative condylectomy in the treatment of condylar osteochondroma through an intraoral approach. Int J Oral Maxillofac Surg, 2013, 42: 1582–1586.
6. Yu H, Jiao F, Li B, *et al*. Endoscope-assisted conservative condylectomy combined with orthognathic surgery in the treatment of mandibular condylar osteochondroma. J Craniofac Surg, 2014, 25: 1379–1382.
7. Shen ML, Yu JS, Yu HB, *et al*. Establishment and application of a

digital workflow in the treatment of condylar osteochondroma and secondary dentofacial deformities using image-guided endoscopic navigation combined with orthognathic surgery. Chin J Stomatol (Chinese), 2016, 51: 728–733.
8. Bernard SA, Murphey MD, Flemming DJ, *et al*. Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging. Radiology, 2010, 255: 857–865.
9. Muñoz M, Goizueta C, Gil-Díez JL, *et al*. Osteocartilaginous exostosis of the mandibular condyle misdiagnosed as temporomandibular joint dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1998, 85: 494–495.
10. Meng Q, Chen S, Long X, *et al*. The clinical and radiographic characteristics of condylar osteochondroma. Oral Surg Oral Med Oral Pathol Oral Radiol, 2012, 114: e66–e74.
11. Koga M, Toyofuku S, Nakamura Y, *et al*. Osteochondroma in the mandibular condyle that caused facial asymmetry: a case report. Cranio, 2006, 24: 67–70.
12. Peroz I, Scholman HJ, Hell B. Osteochondroma of the mandibular condyle: a case report. Int J Oral Maxillofac Surg, 2002, 31: 455–456.
13. Huang D, He DM, Yang C, *et al*. Computer-assisted local resection for exostosis osteochondroma of the mandibular condyle. J Craniofac Surg, 2013, 24: e446–e449.
14. Zhang J, Wang H, Li X, *et al*. Osteochondromas of the mandibular condyle: variance in radiographic appearance on panoramic radiographs. Dentomaxillofac Radiol, 2008, 37: 154–160.
15. González-Otero S, Navarro-Cuéllar C, Escrig-de Teigeiro M, *et al*. Osteochondroma of the mandibular condyle: Resection and reconstruction using vertical sliding osteotomy of the mandibular ramus. Med Oral Patol Oral Cir Bucal, 2009, 14: E194–E197.
16. Kim SG, Lim H, Chang CN, *et al*. Jaw deviation and ankylosis caused by condylar osteochondroma: long-term treatment outcome. J Oral Maxillofac Surg, 2014, 72: 604.
17. Woertler K, Lindner N, Gosheger G, *et al*. Osteochondroma: MR imaging of tumor-related complications. Eur Radiol, 2000, 10: 832–840.
18. Lee JK, Yao L, Wirth CR. MR imaging of solitary osteochondromas: report of eight cases. AJR Am J Roentgenol, 1987, 149: 557–560.
19. Sato K, Kodera T, Kitai R, et al. Osteochondroma of the skull base: MRI and histological correlation. Neuroradiology, 1996, 38: 41–43.
20. Buoncristiani RD, Casagrande A, Felsenfeld AL. Osteochondroma of the glenoid fossa: occurrence in an atypical location. J Oral Maxillofac Surg, 2003, 61: 134–137.
21. Tanaka T, Morimoto Y, Masumi S, *et al*. Utility of frequency-selective fat saturation T2-weighted MR images for the detection of joint effusion in the temporomandibular joint. Dentomaxillofac Radiol, 2002, 31: 305–312.
22. Iwata T, Kawata T. Preoperative and postoperative examination of occlusal and maxillofacial changes after osteochondroma extirpation. Am J Orthod Dentofacial Orthop, 2016, 149: 259–268.

DOI 10.1007/s10330-018-0272-2
Cite this article as: Shen ML, Yu HB, Zhu L, *et al*. Comparison of computed tomography and magnetic resonance imaging for the detection of mandibular condylar osteochondroma. Oncol Transl Med, 2018, 4: 108–115.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0283-3

June 2018, Vol. 4, No. 3, P116–P119

Guideline Obeservation

Updates in version 2.2018 of the NCCN guidelines for esophageal and esophagogastric junction cancers

Liu Huang (✉)

Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Comment

Preferred Regimens provide by expert group were adjusted: (1) Fluorouracil and cisplatin was no longer the Preferred Regimen for Preoperative Chemoradiation and Perioperative Chemotherapy (recommended as the other regimens); (2) DCF modifications were no longer the Preferred Regimens for First-Line Therapy (recommended as the other regimens); (3) Pembrolizumab (For second-line or subsequent therapy for MSI-H or dMMR tumors) was recommended as the Preferred Regimen for Second-Line or Subsequent Therapy; (4) Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) was no longer the Preferred Regimen for Second-Line or Subsequent Therapy. Survivors who underwent esophagectomy are at particular risk for clinically relevant long-term health issues, especially GI-related issues, such as malnutrition, dysphagia, dumping syndrome, delayed gastric emptying, reflux, and fatigue, which have been shown to negatively impact survivors' quality of life. This update proposes the following specific management and monitoring solutions for esophageal cancer survivors: Weight monitoring and the nutritional status in patients with esophageal cancer who underwent surgery are important. Intervention by nutrition specialists is recommended. Treatment of postoperative complications, such as delayed gastric emptying, dumping syndrome, esophageal bile reflux, and dysphagia should be carefully considered, and nursing advice should also be provided. In patients who previously had hypertension, the blood pressure condition may be improved after weight loss. Therefore, blood pressure should be monitored, and the original antihypertensive regimen adjusted as appropriate. Patients who previously had diabetes and hyperlipidemia may also need similar adjustments. Complications caused by chemoradiotherapy, such as radiation-induced heart injuries and chemotherapy-induced neuropathy, should be managed. Patient's psychological and physical states should be evaluated. Healthy lifestyle: Specific advice on dietary habits, living habits, physical activities, smoking cessation, and alcohol abstinence is necessary.

Received: 11 June 2018
Revised: 26 June 2018
Accepted: 29 June 2018

Updates in version 2.2018 from version 1.2018

ESOPH-F principles of systemic therapy

The NCCN Categories of Preference has been applied to all of the suggested treatment regimens.

The regimen and dosing schedule pages were updated to reflect the changes noted above.

ESOPH-J principles of survivorship

This is a new section that provides recommendations for survivorship including Management of long-term sequelae of disease or treatment, Counseling regarding health behaviors, Cancer screening recommendations (for average risk survivors), and Survivorship care planning and coordination.

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in version 1.2018 from version 4.2017

Workup

PET/CT evaluation , from skull base to mid-thigh, if no evidence of M1 disease.

✉ Correspondence to: Liu Huang. Email: huangliu017@163.com

Adenocarcinomas

Primary Treatment Options for Medically Fit Patients: For cT4b the following option was added, "Consider chemotherapy alone in the setting of invasion of trachea, great vessels, or heart".

For patients who have received preoperative chemoradiation or chemotherapy, if R1 resection: Added "Observation until progression"as an option.

"Chemotherapy if received preoperatively" was removed.

Squamous cell carcinoma and adenocarcinoma

Management of non-surgical candidates: cT1b-T4a N0–N+ or cT4b (unresectable); able to tolerate chemoradiation: "Definitive chemoradiation (50–50.4 Gy of RT + concurrent chemotherapy), removed "Fluoropyrimidine- or taxane-based".

Follow-up / Surveillan

"Imaging studies and Upper GI endoscopy and biopsy as clinically indicated".

Palliative management

"Locoregional recurrence: Prior esophagectomy, no prior chemoradiation" pathway: Revised, still recommend "Concurrent chemoradiation" , but deleted the recommendation of Fluoropyrimidine- or taxane-based regimen.

Principles of pathologic review and biomarker testing

Title revised as "Principles of Pathologic Review and Biomarker Testing"

This section was extensively revised and includes new recommendations for "Microsatellite Instability (MSI) or Mismatch Repair (MMR)Testing" and "PD-L1 Testing."

Principles of systemic therapy

Perioperative chemotherapy revisions: "Fluoropyrimidine and oxaliplatin" changed to a referred option; "Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)" added as an option with corresponding footnote, "Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit".

The following regimens were removed: ECF (epirubicin, cisplatin, and fluorouracil) (category 2B); ECF modifications (category 2B for all modifications)

– Epirubicin, oxaliplatin, and fluorouracil
– Epirubicin, cisplatin, and capecitabine
– Epirubicin, oxaliplatin, and capecitabine

The regimen and dosing schedule pages were updated to reflect the changes on ESOPH-F 2 of 12, for exzample, added regimen of Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT).

Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 h on Day 1; Leucovorin 200 mg/m^2 IV on Day 1; Oxaliplatin 85 mg/m^2 IV on Day 1; Docetaxel 50 mg/m^2 IV on Day 1; Cycled every 14 days for 4 cycles preoperatively and 4 cycles postoperatively for a total of 8 cycles.

Principles of surveillance

First bullet revised: "The surveillance strategies after successful local therapy for esophageal and EGJ cancers remain controversial, with no high-level evidence to guide development of algorithms that balance benefits and risks (including cost) within this cohort."

T1b, Any N; Esophagectomy: Revised recommendation, "Imaging (CT chest/abdomen with contrast unless contraindicated) should be considered starting every 12 months for up to 3 years if the patient is likely to tolerate additional curative-intent therapy for recurrence. EGD as

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Microsatellite Instability (MSI)* or Mismatch Repair (MMR)* Testing

- **MMR or MSI testing should be considered on locally advanced, recurrent, or metastatic esophageal adenocarcinoma or EGJ,[12] in patients who are candidates for treatment with PD-1 inhibitors. The testing is performed on formalin-fixed paraffin-embedded tissue and results are interpreted as MSI-high or mismatch protein repair-deficient in accordance with guidelines for colorectal cancer specimens. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal. MMR or MSI testing should be performed only in CLIA-approved laboratories.**

PD-L1 Testing

- **PD-L1 testing may be considered on locally advanced, recurrent, or metastatic esophageal adenocarcinoma in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test for use on formalin-fixed paraffin-embedded tissue is available as an aid in identifying gastroesophageal junction adenocarcinoma patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.**
- **Assessment of PD-L1 Protein Expression in Esophageal and Esophagogastric Junction Cancers**
  - **This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissues from esophageal or EGJ adenocarcinoma. A minimum of 100 tumor cells must be present in the PD-L1–stained slide for the specimen to be considered adequate for PD-L1 evaluation. A specimen is considered to have PD-L1 expression if the Combined Positive Score (CPS) ≥ 1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.**

needed....".

T2–T4, N0–N+, T4b; Bimodality therapy (definitive chemoradiation): Revised recommendation, "Imaging studies (CT chest/abdomen with contrast unless contraindicated) should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence.

T2–T4, N0–N+, T4b; Trimodality therapy: Recommendation revised, "Imaging studies (CT chest/abdomen with contrast unless contraindicated) should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence.

Staging

The AJCC 7th Edition Cancer Staging Tables were updated to the 8th edition.

T4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum, of which, azygos vein and peritoneum was added new.

T4b: Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway, of which, use "airway" instead of "trachea , etc."

Definition of Histologic Grade (G) of adenocarcinoma is the same with that of squamous cell carcinoma.

Definition of histologic grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Squamous Cell Carcinoma: Definition of Location (L) is new, and the Location is defined by the position of the epicenter of the tumor in the esophagus.

Location category	Location criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azyos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

Note: Location is defined by the position of the epicenter of the tumor in the esophagus

PROGNOSTIC STAGE GROUPS of Clinical Staging (cTNM), Pathological (pTNM), Postneoadjuvant Therapy (ypTNM) are widly revised.

For Squamous Cell Carcinoma

Clinical staging (cTNM)

	c T	c N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0–1	M0
Stage II	T2	N0–1	M0
	T3	N0	M0
Stage III	T3	N1	M0
	T1–3	N2	M0
Stage IVA	T4	N0–2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	p T	p N	M	G	Location
Stage 0	Tis	N0	M0	N/A	Any
Stage IA	T1a	N0	M0	G1	Any
	T1a	N0	M0	GX	Any
Stage IB	T1a	N0	M0	G2–3	Any
	T1b	N0	M0	G1–3	Any
	T1b	N0	M0	GX	Any
	T2	N0	M0	G1	Any
Stage IIA	T2	N0	M0	G2–3	Any
	T2	N0	M0	GX	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
Stage IIB	T3	N0	M0	G2–3	Upper/middle
	T3	N0	M0	GX	Any
	T3	N0	M0	Any	Location X
	T1	N1	M0	Any	Any
Stage IIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIB	T2	N2	M0	Any	Any
	T3	N1–2	M0	Any	Any
	T4a	N0–1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0–2	M0	Any	Any
	Any T	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Postneoadjuvant therapy (ypTNM)

	yp T	yp N	M
Stage I	T0–2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0–2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1–2	M0
	T4a	NX	M0
	T4b	N0–2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

For Adenocarcinoma

Clinical staging (cTNM)

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
	T3	N0–1	M0
	T4a	N0–1	M0
Stage IVA	T1–4a	N2	M0
	T4b	N0–2	M0
	Any T	N3	M0
Stage IVB	any T	Any N	M1

Pathological (pTNM)

	p T	p N	M	G
Stage 0	Tis	N0	M0	N/A
Stage IA	T1a	N0	M0	G1
	T1a	N0	M0	GX
Stage IB	T1a	N0	M0	G2
	T1b	N0	M0	G1–2
	T1b	N0	M0	GX
Stage IB	T1	N0	M0	G3
	T2	N0	M0	G1–2
Stage IIA	T2	N0	M0	G3
	T2	N0	M0	GX
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1–2	M0	Any
	T4a	N0–1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0–2	M0	Any
	Any T	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Postneoadjuvant therapy (ypTNM)

	yp T	yp N	M
Stage I	T0	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1–2	M0
	T4a	NX	M0
	T4b	N0–2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

DOI 10.1007/s10330-018-0283-3
Cite this article as: Huang L. Updates in version 2.2018 of the NCCN guidelines for esophageal and esophagogastric junction cancers. Oncol Transl Med, 2018, 4: 116–119.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0284-4

June 2018, Vol. 4, No. 3, P120–P123

Guideline Obeservation

Updates in version 2.2018 of the NCCN guidelines for gastric cancer

Liu Huang (✉)

Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Comment

Preferred Regimen provides by expert group is adjusted: (1) Fluorouracil and cisplatin was no longer the Preferred Regimen for Preoperative Chemoradiation and Perioperative Chemotherapy (recommended as the other regimens); (2) Pembrolizumab (For second-line or subsequent therapy for MSI-H or dMMR tumors) was recommended as the Preferred Regimen for Second-Line or Subsequent Therapy; (3) Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) was no longer the Preferred Regimen for Second-Line or Subsequent Therapy. The NCCN guidelines recommend that PET/CT is used for preoperative staging due to its greater accuracy than either PET or CT alone. It helps identify M1 patients, distinguish local lesions in the early course from those in the late course of the disease, and screen appropriate candidates for surgical treatments. However, preoperative PET/CT assessment for gastric cancer has a long way to go before it can be routinely performed in our country because CT assessment remains the first choice in most cases. Nevertheless, PET/CT is worth recommending to patients with difficult staging situations. The indications for neoadjuvant treatment are still highly controversial among Eastern and Western countries. A common status quo in our country is that more aggressive surgeries are performed with a low proportion of cases receiving preoperative radiochemotherapy. Phase III MAGIC trial, compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone, established that perioperative chemotherapy improved OS and PFS in patients with non-metastatic stage II and higher gastric and EGJ adenocarcinoma. In the FNCLCC ACCORD 07 trial (n = 224 patients; 25% had gastric adenocarcinoma), Ychou *et al* reported that perioperative chemotherapy with fluorouracil and cisplatin (2 or 3 preoperative cycles and 3 or 4 postoperative cycles) significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer. Phase II/III AIO-FLOT4 trial, Al-Batran et al compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen with a primary endpoint of pCR of the primary tumor. FLOT was associated with significantly higher proportions of patients achieving pCR than was ECF (16%; 95% CI, 10–23 vs. 6%; 95% CI, 3–11; P = 0.02). Additionally, FLOT was associated with a reduction in the percentage of patients experiencing at least one grade 3–4 adverse event. Although the NCCN guidelines recommend that patients with T2 stage or higher gastric cancer should prioritize perioperative chemotherapy + surgery, a treatment model of surgery + postoperative adjuvant therapy is more common in China. Therefore, the preoperative MDT discussion and a strengthened collaboration among the Departments of Surgery, Oncology, and Imaging are helpful and most important in optimizing patients' treatment plans. The recommendations of the NCCN guidelines for preoperative radiochemotherapy for gastric cancer are primarily based on the results of the CROSS study, which mainly enrolled patients with esophageal carcinoma and adenocarcinoma of the esophagogastric junction. Therefore, the recommendation level for preoperative radiochemotherapy in gastric cancer is not as high as that for perioperative chemotherapy, and more advanced evidence should be expected. In addition, special attention should be paid to the prevention and treatment of adverse reactions of the three-drug combination scheme. Even in the western population, the tolerability of the preoperative ECF/DCF/FLOT regimen remains worrisome; thus, optimization of the regimen and identification of appropriate candidates among the population should be implemented in the future.This edition of the guidelines adds a reasonable assessment on the efficacy of preoperative radiochemotherapy and emphasizes that patients who cannot achieve R0 resection after preoperative radiochemotherapy or who have undergone metastases during preoperative radiochemotherapy should be subjected to palliative supportive care.

Received: 11 June 2018
Revised: 26 June 2018
Accepted: 29 June 2018

✉ Correspondence to: Liu Huang. Email: huangliu017@163.com

Comment

We believe that failure of radiochemotherapy in these patients may indicate that the disease itself is highly invasive and has a poor prognosis. To some extent, if the metastases occur during preoperative radiochemotherapy, these patients may also suffer from tumor recurrence and metastasis long before they are directly treated with surgeries without neoadjuvant therapy. Therefore, preoperative radiochemotherapy can prevent unnecessary surgeries in this group of patients. However, this point of view remains an idea because designing a controlled clinical study to confirm it is currently impractical, and patients with limited-stage gastric cancer who would present metastases immediately after the surgery cannot be identified beforehand. However, we know that, as a whole, preoperative radiochemotherapy does increase the overall survival in patients with T2 stage or higher gastric cancer. Several questions, such as the optimization of preoperative radiochemotherapy regimens, value of immunotherapy in neoadjuvant therapy, and more accurate screening methods in identifying patients who can benefit from preoperative radiochemotherapy, are still worth studying.

MSI (dMMR) and PD-L1, following HER2, have become the recommended detection markers for advanced gastric cancer and are used to guide the application of anti-PD-1/PD-L1 immune checkpoint inhibitors. Currently, the primary existing problem is that the testing standards for MSI and PD-L1 have not been established, followed by the lack of qualification standards for the testing centers. Second, in addition to patients with advanced stage gastric cancer, the therapeutic value of the drug should be explored in the perioperative population.

The strict procedures for the comprehensive management of hereditary gastric cancer in our country are lacking, and preventive total gastrectomy has not been actively recommended and accepted. In this regard, patient and family education and collection of their pedigree data are necessary. Patients who have not undergone tumor resection should be strictly and regularly monitored.

Updates in Version 2.2018 of the NCCN guidelines for Gastric Cancer from Version 1.2018

GAST-F principles of systemic therapy

The NCCN Categories of Preference has been applied to all of the suggested treatment regimens.

The regimen and dosing schedule pages were updated to reflect the changes noted above.

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in version 1.2018 of the NCCN guidelines for gastric cancer from version 5.2017

Workup

PET/CT evaluation, from skull base to mid-thigh, if no evidence of M1 disease.

Endoscopic ultrasound (EUS) if early stage disease suspected or if early versus locally advanced disease needs to be determined (preferred).

Primary treatment

Medically fit, potentially resectable; cT2 or higher, Any N: "Perioperative chemotherapy (category 1)" changed to a preferred recommendation.

After perioperative chemotherapy and preoperative chemoradiation, a new "Response Assessment" pathway (GAST-3) was added. Previously surgery was recommended for these patients.

Surgically unresectable: Systemic therapy added as an option.

Postoperative management for patients who have not received preoperative chemotherapy or chemoradiation

R0 resection; pT3, pT4, Any N or Any pT, N+:

Revised, "Fluoropyrimidine (fluorouracil or capecitabine), then fluoropyrimidine-based chemoradiation, then fluoropyrimidine (fluorouracil or capecitabine), if less than a D2 dissection (category 1)."

"Chemotherapy for patients who have undergone primary D2 lymph node dissection" changed from a category 2A to category 1.

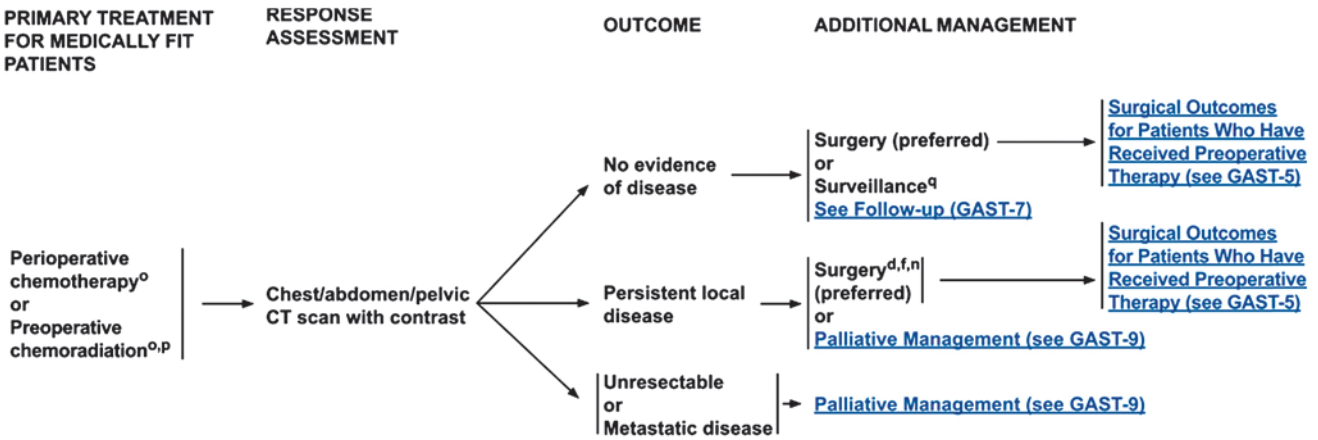
Follow-up/Surveillance

"Monitor for nutritional deficiency (eg, B12 and iron) in surgically resected patients (especially after total gastrectomy) and treat as indicated".

P stage II/III or yp stage I-III (treated with neoadjuvant ± adjuvant therapy); Fourth bullet revised: "CT chest/abdomen/pelvis with oral and IV contrast every 6–12 months for first 2 years, then annually up to 5 years and/or can consider PET/CT as clinically indicated"

Palliative management

Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2: "Chemoradiation (only if locally



Microsatellite Instability (MSI)* or Mismatch Repair (MMR)[d] Testing

- MMR or MSI testing should be considered on locally advanced, recurrent, or metastatic gastric carcinoma,[7] in patients who are candidates for treatment with PD-1 inhibitors. The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high or mismatch protein repair-deficient in accordance with guidelines for colorectal cancer specimens. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal. MMR or MSI testing should be performed only in CLIA-approved laboratories.

PD-L1 Testing

- PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric carcinomas in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test for use on FFPE tissue is available as an aid in identifying gastric and gastroesophageal junction adenocarcinoma patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.
- Assessment of PD-L1 Protein Expression in Gastric Cancers
  - This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in FFPE tissues from gastric adenocarcinoma. A specimen is considered to have PD-L1 expression if the Combined Positive Score (CPS) ≥1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

unresectable and not previously received)" added as an option.

For both pathways, revised, " Best supportive care" instead of "Palliative care".

Principles of pathologic review and biomarker testing

Title revised, "Principles of Pathologic Review and Biomarker Testing".

This section was extensively revised and includes new recommendations for "Microsatellite Instability (MSI) or Mismatch Repair (MMR)Testing" and "PD-L1 Testing".

Principles of genetic risk assessment

Surveillance recommendations

Hereditary diffuse gastric cancer: Revised, "Prophylactic total gastrectomy is recommended between ages 18 and 40 for CDH1 mutation carriers. A baseline endoscopy is indicated prior to prophylactic total gastrectomy. Intraoperative frozen sections should be..."

Lynch syndrome (LS): "Selected individuals or families or those of Asian descent may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum). See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.

Principles of systemic therapy

Perioperative chemotherapy revisions

"Fluoropyrimidine and oxaliplatin" changed to a preferred option.

"Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)" added as an option with corresponding footnote, "Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit".

The following regimens were removed:

ECF (epirubicin, cisplatin, and fluorouracil) (category 2B).

ECF modifications (category 2B for all modifications)

– Epirubicin, oxaliplatin, and fluorouracil

– Epirubicin, cisplatin, and capecitabine

– Epirubicin, oxaliplatin, and capecitabine

The regimen and dosing schedule pages were updated to reflect the changes on GAST-2 of 11 and GAST-F 3 of 11.

Staging

The AJCC 7th Edition Cancer Staging Tables were updated to the 8th edition.

Definitions of Histologic Grade (G) was revised.

Definitions of histologic grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

AJCC PROGNOSTIC STAGE GROUPS were added.

Clinical staging (cTNM)

	c T	c N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T1	N1, N2, or N3	M0
	T2	N1, N2, or N3	M0
Stage IIB	T3	N0	M0
	T4a	N0	M0
Stage III	T3	N1, N2, or N3	M0
	T4a	N1, N2, or N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

		p T	p N	M
Stage 0		Tis	N0	M0
Stage IA		T1	N0	M0
Stage IB		T1	N1	M0
		T2	N0	M0
Stage IIA		T1	N2	M0
		T2	N1	M0
		T3	N0	M0
Stage IIB	T1		N3a	M0
		T2	N2	M0
		T3	N1	M0
		T4a	N0	M0
Stage IIA	T2		N3a	M0
		T3	N2	M0
		T4a	N1 or N2	M0
		T4b	N0	M0
Stage IIB	T1		N3b	M0
		T2	N3b	M0
		T3	N3a	M0
		T4a	N3a	M0
		T4b	N1 or N2	M0
Stage IIC		T3	N3b	M0
		T4a	N3b	M0
		T4b	N3a or N3b	M0
Stage IV		Any T	Any N	M1

Pos-neoadjuvant therapy (ypTNM)

	yp T	yp N	M
Stage I	T1	N0	M0
	T2	N0	M0
	T1	N1	M0
Stage II	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage III	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

DOI 10.1007/s10330-018-0284-4
Cite this article as: Huang L. Updates in version 2.2018 of the NCCN guidelines for gastric cancer. Oncol Transl Med, 2018, 4: 120–123.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0275-5
June 2018, Vol. 4, No. 3, P124–P127

CASE REPORT

Recurrent ascites due to spontaneous intraperitoneal bladder rupture after pelvic radiation therapy for cervical cancer

Qian Shen[1], Yuping Yin[2], Lihong Zhang[1], Dongbo Liu[1], Shiying Yu[1], Huihua Xiong[1], Xianglin Yuan[1], Yongsheng Jiang[1] (✉)

[1] Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[2] Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract

Radiation cystitis is one of the major complications after radiotherapy in cervical cancer patients. However, spontaneous intraperitoneal bladder rupture resulting from radiation cystitis after radiotherapy for cervical cancer is extremely rare. We report a 52-year-old patient who received radiation therapy for cervical cancer 15 years ago. Since the last 8 years, the patient frequently presented with recurrent abdominal distension, oliguria, and ascites. Ascitic fluid drainage and supportive treatment provided symptomatic relief. However, every few months, the symptoms recurred. The patient was subjected to exploratory laparotomy twice. The first exploratory laparotomy in July 2015 revealed no significant abnormalities. During the second exploratory laparotomy in November 2016, intraperitoneal bladder rupture was observed, and the patient underwent surgical repair. After the surgery, ascites was completely cured. The occurrence of spontaneous intraperitoneal bladder rupture after radiation therapy in cervical cancer patients is rare. The prognosis for the condition is good if it is promptly diagnosed and treated.

Received: 25 May 2018
Revised: 5 June 2018
Accepted: 10 June 2018

Key words: radiation cystitis; spontaneous intraperitoneal bladder rupture; recurrent ascites; cervical cancer

The rupture of the urinary bladder is usually associated with trauma, chronic diseases of the bladder, or bladder outflow obstruction. Non-traumatic, spontaneous intraperitoneal bladder rupture, which is associated with pelvic radiation therapy, is rare in cervical cancer patients. The diagnosis of urinary bladder rupture might be difficult due to inconsistent history and variable presentation. Spontaneous intraperitoneal bladder rupture is often misdiagnosed initially, and at times, it can be a life-threatening event.

Case presentation

A 52-year-old woman presented to the hospital with abdominal distension, oliguria, and ascites for the first time in January 2010. She denied any history of trauma. She had a history of cervical cancer in 2003 and had undergone extensive hysterectomy and pelvic lymph node dissection on March 24, 2003, which revealed squamous carcinoma of the cervix (stage IIb). She received postoperative concurrent pelvic chemoradiotherapy, including pelvic radiation Dt 4600 cGy/23 F and brachytherapy Dt 1700 cGy/3 F, and was regularly followed up. After a 5-year follow-up period, there was no recurrence, and the patient was asymptomatic; thus, regular follow-up was discontinued.

At the time of admission in January 2010, 7 years since the diagnosis of cervical cancer, the patient had abdominal distension and pain, decrease in the urine output, and significant ascites. On examination, the temperature, blood pressure, and heart rate were all normal. Chest auscultation revealed a regular heart

✉ Correspondence to: Yongsheng Jiang. Email: ysjiang.china@163.com

beat without murmur, and clear breath sounds without crackles. The abdomen was grossly distended with free fluid, and with hypoactive bowel sounds. There were no features suggestive of peritonitis, no enlarged liver or spleen on palpation, and no percussion pain in the region of the kidney. No abnormalities were found on gynecologic examination. The diagnosis at admission was ascites of unknown origin and cervical cancer. Laboratory findings were as follows: Serum BUN and creatinine levels were slightly elevated. Complete blood cell count, liver function, and coagulation battery test results were normal, and the tumor marker levels, including those of carcinoembryonic antigen, squamous cell carcinoma antigen, CA153, CA125, and CA199, were also normal. Ultrasound examination indicated a rough bladder wall and a large amount of abdominal and pelvic effusion. Computed tomography (CT) showed a large amount of ascites without any evidence of malignancy or obstruction. No obvious abnormalities were found on cystoscopy, except for a pale bladder mucosa. PET-CT showed an abnormally increased uptake of 18F-FDG diffused in both the abdominal and pelvic cavities, which could be due to metastatic lesions. Routine biochemical tests and pathological examination of the ascitic fluid revealed the presence of red blood cells, lymphocytes, and mesothelium cells but no cancer cells. The patient was diagnosed with incomplete malignant bowel obstruction, and after symptomatic and supportive treatment, she was discharged after improvement. During the period 2010 to 2015, the patient had recurrent abdominal pain and distension, with varying amounts of ascitic fluid accumulation. No obvious abnormalities were found on the CT scans and cystoscopies. The symptoms were relieved after ascitic fluid drainage and supportive treatment.

In July 2015, the patient was admitted again with the same symptoms, including abdominal pain, lower abdominal distension, and oliguria. PET/CT examination showed no particular abnormalities. A multidisciplinary team (MDT), consisting of an oncologist, gynecologist, gastroenterologist, and radiologist took a decision to perform a laparoscopic exploration; however, no obvious abnormality was found during the procedure. Between 2015 and 2016, the patient experienced intermittent abdominal pain and a large amount of ascites. Symptoms usually occurred without an apparent cause. There were no specific treatment measures, except ascitic fluid drainage and symptomatic and supportive treatment, since the cause of ascites could not be identified. In November 2016, the patient presented with the same symptoms again, and after consultation by the MDT, underwent exploratory laparotomy for the second time. The bladder wall was found to be extremely thin, and a very tiny crevice was found on the wall. After the repair of the ruptured bladder, the patient was cured and has not experienced ascites since then.

Discussion

Our case highlights three interconnected phenomena: radiation cystitis, recurrent ascites, and spontaneous bladder rupture.

Radiation cystitis is a common complication after pelvic radiotherapy for cervical cancer [1]. According to the time of occurrence and severity, radiation cystitis can be divided into three types: acute radiation cystitis, chronic radiation cystitis, and radiation bladder fistula [2–3]. Acute radiation cystitis occurs during or soon after radiation treatment usually within 6 months. It usually presents as increased urinary frequency and urgency, with gross or microscopic hematuria [4], which is usually self-limiting, and is generally managed conservatively [5]. Chronic radiation cystitis, which accounts for 80% of the cases of radiation cystitis [6], can develop from 6 months to 20 years after radiation therapy. The main presenting symptom is hematuria, which might vary from mild to severe life-threatening hemorrhage [5, 7]. Radiation bladder fistula, which is often associated with the distribution of radiation dose, can occur in some severe cases.

Spontaneous intraperitoneal bladder rupture is rare in cervical cancer patients who undergo radiation therapy, but can be life threatening at times [8]. The most common causes of bladder rupture are blunt trauma, chronic diseases of the urinary bladder, or bladder outflow obstruction; other possible reasons include surgical procedures and irradiation to the pelvis [9-12]. Accurate diagnosis of spontaneous intraperitoneal bladder rupture before surgery is difficult and the surgery is often delayed in the absence of a history of trauma or preexisting chronic bladder disease. Symptoms and signs of spontaneous intraperitoneal bladder rupture can be non-specific and misleading [13-15]. Patients usually present with an acute abdomen, abdominal distension, oliguria/dysuria, and hematuria [12–13]. Symptoms might be insidious on onset, presenting as only ascites or acute renal failure [14, 16-18]. Ultrasonography and CT scans might miss most cases of intraperitoneal bladder rupture. CT cystography might be useful to identify the rupture of the bladder, but it is difficult to locate a minute breach [19]. The gold standard for the diagnosis of intraperitoneal bladder rupture is exploratory laparotomy. However, this is an invasive procedure for a patient without serious complications. Measuring the urea and creatinine levels in the ascitic fluid and serum is a simple and non-invasive diagnostic test, and an ascites-to-serum creatinine ratio > 1.0 usually highly supports the diagnosis of spontaneous intraperitoneal bladder rupture [20–21]. The conservative treatment for spontaneous intraperitoneal

bladder rupture comprises antibiotics and percutaneous peritoneal drainage for patients with a history of pelvic irradiation [22–23]. For recurrent cases or patients with severe symptoms after ineffective conservative therapy, immediate surgery with repair of the urinary bladder in 2 layers is strongly recommended [24–25]. After bladder repair, prolonged drainage is required, and the patients must be educated to avoid bladder overdistension because of the increased risk of re-perforation [26].

As described by Addar et al. in 1996 [27], the treatment for spontaneous bladder rupture must be individualized based on the following 6 principles: (1) defect must be identified and confirmed; (2) peritoneal cavity should be thoroughly lavaged; (3) defect should be widely excised; (4) reconstitution of the intact bladder should be performed with tissue having an intact blood supply, especially in the case of an irradiated tissue; (5) support adequate healing by prolonged bladder drainage and prophylactic antibiotics; and (6) primary or recurrent malignant disease should be excluded.

After 7 years of surgery and radiotherapy, our patient started experiencing intermittent abdominal pain and a large amount of ascites. During the next 6 years, although she underwent cystoscopy, PET/CT examination, and laparotomy, there were no positive findings related to the symptoms. We did not perform a peritoneal fluid analysis of urea and creatinine levels because we did not consider the possibility of a spontaneous intraperitoneal bladder rupture. During the second exploratory laparotomy, the bladder wall of the patient was found to be significantly thin, and there was a minute breach in the local area. After the bladder was repaired in 2 layers, the patient was cured, and since then, the patient has not experienced abdominal pain and ascites again.

This case is clinically rare. The patient was admitted to the hospital repeatedly for 6 years with the chief complaint of recurrent ascites, with no severe peritonitis or acute renal failure. This patient is a dancer, with a habit of delaying micturition, due to occupational reasons. Over-distension is very unfavorable for a bladder that has undergone radiation therapy and can lead to the occurrence of different complications. Since the rupture of the bladder is very minute, accompanied by adhesion of the pelvic tissue after surgery and radiotherapy, the breach is hidden; hence, the cystoscopy and the first laparoscopic exploration failed to detect it.

This case shows that when a cervical cancer patient experiences ascites after radiotherapy, the possibility of bladder rupture should be considered [28]. For patients with complaints of recurrent ascites, cytology and urea and creatinine levels of the ascitic fluid should be tested. Spontaneous intraperitoneal bladder rupture should always be considered in the differential diagnosis of patients who present with abdominal distension, oliguria, and ascites and in whom an increased level of urea/creatinine is detected in the serum and/or peritoneal fluid aspirate [29]. The prognosis for this disease is good if diagnosed and treated promptly.

Conclusion

Spontaneous intraperitoneal bladder rupture is a rare cause of ascites, but when presented with ascites and oliguria of unknown cause, especially in cases with a history of radiation therapy to the pelvis, the possibility of spontaneous intraperitoneal bladder rupture should be considered in the differential diagnosis. To avoid the risk of mortality, prompt and precise diagnosis is mandatory. After proper surgical treatment, the patients must be educated about bladder emptying to prevent overdistension. We hope our case report increases the awareness of spontaneous intraperitoneal bladder rupture, so that these patients can be promptly diagnosed and appropriately treated to achieve the best possible outcomes.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Alesawi AM, El-Hakim A, Zorn KC, *et al*. Radiation-induced hemorrhagic cystitis. Curr Opin Support Palliat Care, 2014. 8: 235–240.
2. Wit EM, Horenblas S. Urological complications after treatment of cervical cancer. Nat Rev Urol, 2014, 11: 110–117.
3. Li F, Guo H, Qiu H, *et al*. Hou, Urological complications after radical hysterectomy with postoperative radiotherapy and radiotherapy alone for cervical cancer. Medicine (Baltimore), 2018. 97: e0173.
4. Corman JM, McClure D, Pritchett R, *et al*. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. J Urol, 2003, 169: 2200–2202.
5. Liem X, Saad F, Delouya G. A practical approach to the management of radiation-induced hemorrhagic cystitis. Drugs, 2015, 75: 1471–1482.
6. Mougin J, Souday V, Martin F, *et al*. Evaluation of hyperbaric oxygen therapy in the treatment of radiation-induced hemorrhagic cystitis. Urology, 2016, 94: 42–46.
7. Tahir AR, Westhuyzen J, Dass J, *et al*. Hyperbaric oxygen therapy for chronic radiation-induced tissue injuries: Australasia's largest study. Asia Pac J Clin Oncol, 2015, 11: 68–77.
8. Limon O, Unluer EE, Unay FC, *et al*. An unusual cause of death: spontaneous urinary bladder perforation. Am J Emerg Med, 2012, 30: 2081.
9. Ketata S, Boulaire JL, Al-Ahdab N, *et al*. Spontaneous intraperitoneal perforation of the bladder: a late complication of radiation therapy for prostate cancer. Clin Genitourin Cancer, 2007, 5: 287–290.
10. Labanaris AP, Zugor V, Reinhold Nutzel R, *et al*. Spontaneous rupture of the urinary bladder 10 years after curative radiotherapy. ScientificWorldJournal, 2008. 8: 405–408.
11. Suzuki T, Usami A, Shinoda M, *et al*. Spontaneous bladder rupture

occurred 17 years after radiation treatment for cervical cancer: a case report. Nihon Shokakibyo Gakkai Zasshi, 2011, 108: 1437–1440.
12. Kivlin D, Ross C, Lester K, *et al*. A case series of spontaneous rupture of the urinary bladder. Curr Urol, 2015, 8: 53–56.
13. Dubey IB, Mohanty D, Jain BK. Diverse presentation of spontaneous rupture of urinary bladder: review of two cases and literature. Am J Emerg Med, 2012, 30: 832.
14. Matsumura M, Ando N, Kumabe A, *et al*. Pseudo-renal failure: bladder rupture with urinary ascites. BMJ Case Rep, 2015, 2015.
15. Sawalmeh H, Al-Ozaibi L, Hussein A, *et al*. Spontaneous rupture of the urinary bladder (SRUB); A case report and review of literature. Int J Surg Case Rep, 2015. 16: 116–118.
16. Bourgeois S, Decupere M, Devriendt D, *et al*. A case of pseudorenal failure - spontaneous rupture of the urinary bladder. Acta Gastroenterol Belg, 2017, 80: 419–421.
17. Mark A, Meister M, Opara B, *et al*. Nontraumatic urinary bladder rupture presenting as renal pseudo-failure and ascites. Radiol Case Rep, 2017, 12: 304–307.
18. Ridinger HA, Kavitt RT, Green JK. Urinary ascites and renal failure from unrecognized bladder rupture. Am J Med, 2012. 125: e1–2.
19. Montigny P, Pringot J, Billemont MF, *et al*. Traumatic urinary bladder rupture: the usefulness of CT cystography. Jbr-btr, 2013, 96: 90.
20. Abirami K, Sivaramakrishna G, Lakshmi AY, *et al*. Urinary ascites. Indian J Nephrol, 2012. 22: 143–144.
21. Arnold WC, Redman JF, Seibert JJ. Analysis of peritoneal fluid in urinary ascites. South Med J, 1986, 79: 591–594.
22. Abu Mahfouz, Sayer IT, Phillips C. Conservative management of spontaneous rupture of the urinary bladder. Int Urogynecol J, 2011, 22: 629–631.
23. Jones AL, Armitage JN, Kastner C. Conservatively managed spontaneous intraperitoneal bladder perforation in a patient with chronic bladder outflow obstruction. Urol Ann, 2014, 6: 370–372.
24. Johnsen NV, Young JB, Reynolds WS, *et al*. Evaluating the role of operative repair of extraperitoneal bladder rupture following blunt pelvic trauma. J Urol, 2016, 195: 661–665.
25. Wakamiya T, Kuramoto T, Inagaki T. Two cases of spontaneous rupture of the urinary bladder associated with radiation cystitis, repaired with omentum covering. Hinyokika Kiyo, 2016, 62: 545–548.
26. Tsai, CH, Wang YC, Wu SC, *et al*. Laparoscopic repair of extraperitoneal urinary bladder rupture after blunt abdominal trauma. Am Surg, 2012, 78: E385–386.
27. Addar MH, Stuart GC, Nation JG, *et al*. Spontaneous rupture of the urinary bladder: a late complication of radiotherapy--case report and review of the literature. Gynecol Oncol, 1996, 62: 314–316.
28. Fujikawa K, Yamamichi F, Nonomura M, *et al*. Spontaneous rupture of the urinary bladder is not a rare complication of radiotherapy for cervical cancer: report of six cases. Gynecol Oncol, 1999, 73: 439–442.
29. Baseman AG, Snodgrass WT. Repeat spontaneous bladder rupture following radiation therapy. J Urol, 2003, 170: 2417.

DOI 10.1007/s10330-018-0275-5
Cite this article as: Shen Q, Yin YP, Zhang LH, *et al*. Recurrent ascites due to spontaneous intraperitoneal bladder rupture after pelvic radiation therapy for cervical cancer. Oncol Transl Med, 2018, 4: 124–127.

Oncology and Translational Medicine
DOI 10.1007/s10330-018-0266-6
June 2018, Vol. 4, No. 3, P128–P131

Case Report

Accidental finding of renal myxoma and a literature review

Yuxiang Hong[1], Qingtao Yang[2] (✉), Junhong Zheng[2], Gaoming Hou[2]

[1] Shantou University Medical College, Shantou 515041, China
[2] Department of Urology, Second Affiliated Hospital of Shantou University Medical College, Shantou 515041, China

Abstract

We present the case of a middle-aged Chinese woman who presented as asymptomatic; however, we found an irregular right renal mass in this patient. She underwent partial nephrectomy after comprehensive evaluation, and she was finally diagnosed with renal myxoma according to pathological and immunohistochemical studies. Myxomas are rare, benign, soft-tissue tumors that mainly occur in the heart and skin, although various anatomical locations have been described. The kidneys are a rare location of myxoma; thus, renal myxomas may easily be misdiagnosed. To date, approximately 17 cases of renal myxoma have been reported in the English literature since 1968. All the patients in these cases underwent nephrectomy as treatment, and were disease-free on follow-up. Postoperative pathology facilitates a decisive diagnosis that differentiates benign from malignant myxoma, which is vital for the following treatment and prognosis.

Received: 3 April 2018
Revised: 10 June 2018
Accepted: 16 June 2018

Key words: kidney; myxoma; neoplasm; urology

Case Report

A 45-year-old woman was hospitalized because of a right renal area mass that was incidentally discovered using abdominal plain and enhanced computed tomography (CT) at her routine health examination. She had no significant past, present, or family history, and her general and systemic examination results were normal. The laboratory examination results, including biochemical and hematological investigations, urinalysis, coagulation, cortisol, and aldosterone, were within normal limits. CT of the abdomen (Fig. 1) demonstrated a low-density mass (52 mm × 44 mm) in the right renal area. After comprehensive condition assessment, case discussions, and receipt of informed consent of the patient, laparoscopic exploratory surgery was performed to verify the actual location of the mass. During the exploratory operation, the mass was found to be located in the right renal upper pole, and laparoscopic right partial nephrectomy was finally performed. The specimen was sent for histopathological and immunohistochemical examinations. The slice surface of the tumor showed a pale yellow, soft, and translucent texture with an intact capsule. Microscopically, the tumor was composed of a large amount of myxoid material and showed scattered distribution of spindle cells and nuclear staining with a wavy pattern (Fig. 2). The results of immunohistochemical analysis showed that the cells stained strongly positive for cluster of differentiation (CD)34 and smooth muscle actin; weakly positive for CD68 and DOG-1; cytokeratin, S-100, B-cell lymphoma-2, and CD99 staining yielded negative results.

According to the histological and immunohistochemical results, renal myxoma was the final pathologic diagnosis. The patient had an uneventful hospital course, and was discharged on the 15th postoperative day.

Discussion

Myxomas are benign neoplasms derived from connective tissue, consisting chiefly of polyhedral and stellate cells that are loosely embedded in a soft mucoid

✉ Correspondence to: Qingtao Yang. Email: yang2001tao@126.com

Table 1 Summary of 17 case reports of renal myxoma

Publish Year	Author	Symptoms	Age/Sex	Site	Size (cm)	Imaging Examination	Treatments
1968 [5]	Appel *et al*	Hematuria for 2 months	No / No	Right parapelvic	8	Excretory urogram: a mass in the upper pole, compressing and obstructing the upper calyceal system Renal angiogram: entirely avascular space occupying lesion in the upper central portion, lesion seemed clearly to be cystic	Enucleation of mass
1973	Shenansky *et al*	Hematuria for 6 months	62 / Male	Right renal lower pole	4	Excretory urogram: right kidney mass with medial displacement of inferior calyx and infundibulum confirmed by retrograde pyelography Arteriography: splaying of the inferior pole vessels within the right kidney but no abnormal vasculature	Nephrectomy
1994	Melamed *et al*	Renal colic	52 / Female	Left renal lower pole	7	Not available	Nephrectomy
1994	Melamed *et al*	Symptomless	68 / Female	Right renal upper pole	10	Not available	Nephrectomy
1995	Kundu *et al*	Hypochondrium mass for 2 months	36 / Male	Left renal parenchymal mass	28	Intravenous urography: huge mass in the left renal area without any dye excreting from the left kidney USG: solid mass (echoic) in the left kidney	Nephrectomy
2005	Val-Bernal *et al*	Symptomless	37 / Male	Right renal capsule	Diameter: 6	Abdominal echography and CT : a solid low density mass in the medium segment of the right kidney. The mass intruded into the perirenal tissue	Nephrectomy
2006	Owari *et al*	Symptomless	62 / Male	Right renal middle portion	Diameter: 8	CT : well-defined mass MRI: T1WI —homogeneous low signal intensity T2WI —heterogeneous high signal intensity	Nephrectomy
2007	Nishimoto *et al*	Symptomless	36 / Male	Left renal lower pole	9 × 7 × 6	CT: low density, slightly enhanced on contrast MRI: T1WI –low signal intensity T2WI: high signal intensity T1C+Gd–homogeneous enhancement	Nephrectomy
2007	Bolat *et al*	Symptomless	27 / Female	Left renal lower pole	15 × 14 × 7	MRI: well-defined semisolid/semicystic mass T1WI: homogeneous low signal intensity T2WI: heterogeneous high signal intensity	Nephrectomy
2010 [6]	Cao Dianbo *et al*	Symptomless	43 / Female	Left renal mid-upper portion	4.9 × 3.1	MSCT: abnormal density mass, 20–40 HU. Edge enhancement	Nephrectomy
2010 [7]	Hakverdi *et al*	Lower urinary tract infection	59 / Male	Right upper pole	Diameter: 6	USG: well-defined mass CT: low density mass	Nephrectomy
2012 [8]	Yildirim *et al*	Dysuria, uninary obstruction and flank pain	82 / Male	Left renal sinus	Diameter: 9	USG: solid, heterogeneously echogenic CT : low density mass	Nephrectomy
2013 [9]	Abhishek Shah *et al*	Symptomless	43 / Female	Left renal mid-upper portion	4.9 × 3.1	CT: round, ill-demarcated, inhomogeneous lesion; Intravenous contrast: circular septal enhancement and ill-defined margin	Nephrectomy
2014 [2]	Gomez-Gonzalez C *et al*	Renal insufficiency	29 / Female	Left kidney interpolar region	Diameter: 4.4	MRI: cystic lesion T1WI: low intense mass T2WI: hyperintense mass	Nephrectomy
2015 [4]	KamleSh S. Suthar *et al*	right side dull-aching abdominal pain	48 / Female	Right kidney mid and lower pole	6.7 × 6.1 × 7.4	USG : ill-defined hypoechoic mass; CT: hypodense well defined mass with exophytic component	Nephrectomy
2017 [3]	Somuah Tenkorang *et al*	right dull flank pain	50 / Female	Right kidney mid-portion	4×3.5	CT : hypodense well-defined mass; slightly enhanced after intravenous contrast measuring 61 HU	Nephrectomy
2017 [10]	Parth Thakker *et al*	abdominal pain	55 / Female	Right kidney upper pole	Diameter: 1.7	CT: hypodense exophytic lesion MRI: Exophytic mass T1WI&T2WI: hypointense mass	Nephrectomy

This table is reorganized and supplemented from the case report published by Abhishek Shah *et al* [9]

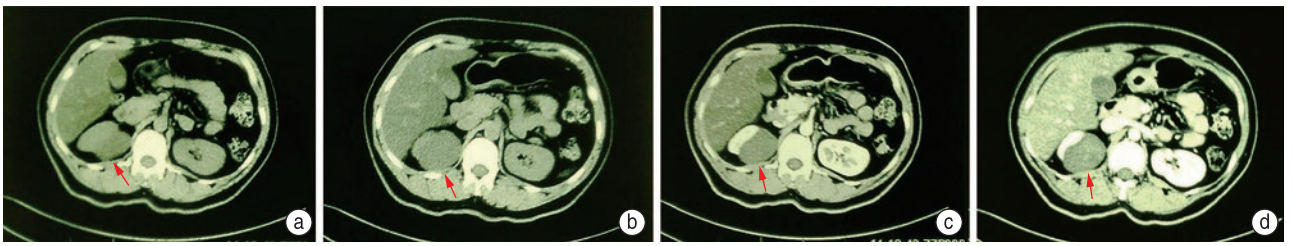


Fig. 1 (a) CT showed a low-density mass (52 mm × 44 mm) can be found in the right adrenal area (the position of the arrow indicating). The edge of the mass was clear and closely related with the right adrenal and right kidney; (b, c and d) The CT scan value is 18 HU, and a contrast-enhanced scan showed progressive enhancement. CT, computed tomography

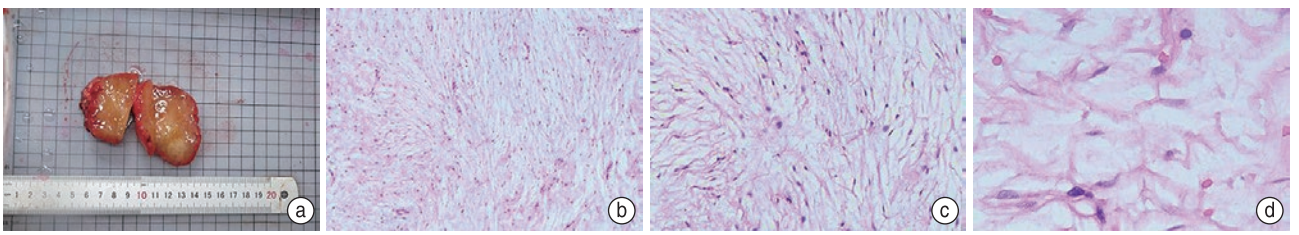


Fig. 2 (a) Pale yellow tumor (7 × 5 × 3 cm), with soft and translucent texture slice surface and intact capsule; (b) HE staining × 40; (c) HE staining × 100; (d) HE staining × 400. Large amount of myxoid material, scattered distribution of spindle cells, nuclear staining with a wavy pattern, and a small number of collagen fibers between the tumor cells were observed

matrix, thereby resembling primitive mesenchymal tissue. They occur frequently intramuscularly, so they may be mistaken for sarcomas. Myxomas are rare, benign, soft-tissue tumors that mainly occur in the heart and skin, although various anatomical locations have been described for these tumors [1].

The kidneys are a rare location of myxomas; thus, renal myxomas may easily be misdiagnosed. Differential diagnoses should be made considering other possible renal benign mesenchymal tumors, such as leiomyomas, hemangiomas, lymphangiomas, neurofibromas, solitary fibrous tumors, schwannomas, and glomus tumors. Furthermore, renal myxomas should also be differentiated from other benign and malignant mesenchymal tumors with myxoid transformation, considering myxoid neurofibromas, myxoid leiomyomas, myxolipomas, and the myxoid variant of malignant fibrous histiocytomas [2].

The kidneys are an unusual location of myxoma; to date, approximately 17 cases of renal myxoma have been reported in the English literature since 1968. Except for our case, the data of 12 cases were summarized in a case report in January 2013, and 5 more cases have been reported since 2013. We reorganized the data of these 17 cases in Table 1. Documented cases of this tumor have shown no difference between men and women; most of the reported patients were asymptomatic and diagnosed incidentally, and few patients had abdominal pain [3].

Radiological methods like ultrasonography, CT, and magnetic resonance imaging are helpful in diagnosis and management. Due to the suspicion of malignancy in these tumors, radical nephrectomy is usually performed, like in our case [4].

Renal myxoma is a benign tumor and usually an incidental finding. Radiographic studies play an important role in differential diagnosis, while also providing reference values in choosing surgical procedures and accurate positioning during the surgery. The postoperative pathology facilitates a decisive diagnosis that differentiates benign from malignant myxoma, which is vital for the following treatment and prognosis.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Durgut K, Onoglu R, Gormus N. Primary cardiac myxomas: report of 28 cases and review the literature. J BUON, 2011, 16: 345–348.
2. Gomez-Gonzalez C, Moreno-Nieto V, Vicente-Pablos M, *et al*. Renal myxoma: an unexpected differential diagnosis. Pol J Pathol, 2014, 65: 157–159.
3. Tenkorang S, Kharbach Y, Omana JP *et al*. Myxoma of the kidney – an unusual benign renal tumor: a case report. J Med Case Rep, 2017, 11: 41.
4. Suthar KS, Vanikar AV, Patel RD, *et al*. Renal myxoma – a rare variety of benign genitourinary tumour. J Clin Diagn Res, 2015, 9: ED11–12.
5. Appel SD, Schoenberg HW. Myxoma of the renal sinus. J Urol, 1968, 100: 254–256.
6. Cao D, Feng C, Xu B, *et al*. Case of renal myxoma associatied with

hemorrhage. Chin J Radiol (Chinese), 2010, 44: 1262.
7. Hakverdi S, Görür S, Yaldız M, *et al*. Renal myxoma: a case report and review of the literature. Turkish J Urol, 2010, 36: 318–321.
8. Yildirim U, Erdem H, Kayikci A, *et al*. Myxoma of the renal sinus: case report and literature review. Turk Patoloji Derg, 2012, 28: 76–79.
9. Shah A, Sun W, Cao D. Myxoma of the kidney associated with hemorrhage. Indian J Surg, 2013, 75: 480–483.
10. Thakker P, Ramsey T, Navarro F. Renal Myxoma, an Incidental Finding. Urol Case Rep, 2017, 13: 131–132.

DOI 10.1007/s10330-018-0266-6
Cite this article as: Hong YX, Yang QT, Zheng JH, *et al*. Accidental finding of renal myxoma and a literature review. Oncol Transl Med, 2018, 4: 128–131.

Oncology and Translational Medicine

Aims & Scope

Oncology and Translational Medicine is an international professional academic periodical. The Journal is designed to report progress in research and the latest findings in domestic and international oncology and translational medicine, to facilitate international academic exchanges, and to promote research in oncology and translational medicine as well as levels of service in clinical practice. The entire journal is published in English for a domestic and international readership.

Copyright

Supervised by

Ministry of Education of the People's Republic of China.

Administered by

Tongji Medical College, Huazhong University of Science and Technology.

Submission information

Manuscripts should be submitted to:
http://otm.tjh.com.cn
dmedizin@sina.com

Subscription information

ISSN edition: 2095-9621
CN: 42-1865/R

■ Subscription rates
Subscription may begin at any time. Remittances made by check, draft or express money order should be made payable to this journal. The price for 2017 is as follows: US $ 30 per issue; RMB ￥28.00 per issue.

Database

Oncology and Translational Medicine is abstracted and indexed in EMBASE, Index Copernicus, Chinese Science and Technology Paper Citation Database (CSTPCD), Chinese Core Journals Database, Chinese Journal Full-text Database (CJFD), Wanfang Data; Weipu Data; Chinese Academic Journal Comprehensive Evaluation Database.

Business correspondence

All matters relating to orders, subscriptions, back issues, offprints, advertisement booking and general enquiries should be addressed to the editorial office.

Mailing address
Editorial office of
Oncology and Translational Medicine
Tongji Hospital
Tongji Medical College
Huazhong University of Science and Technology
Jie Fang Da Dao 1095
430030 Wuhan, China
Tel.: +86-27-69378388
Email: dmedizin@sina.com

Printer
Changjiang Spatial Information Technology Engineering Co., Ltd. (Wuhan) Hangce Information Cartorgraphy Printing Filial, Wuhan, China
Printed in People's Republic of China

Managing director

Jun Xia

Executive editors