

# N2-3 Stage Nasopharyngeal Carcinoma Patients With Cervical Node Necrosis And Extracapsular Spread Benefit From Capecitabine Maintenance Chemotherapy

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## Research

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## Abstract

**Purpose:** The purpose of this study was to analyze the efficacy and toxicities of concurrent chemoradiotherapy plus capecitabine maintenance chemotherapy for N2-3 stage nasopharyngeal carcinoma (NPC) with cervical node necrosis (CNN) and extracapsular spread(ECS).

**Patients and methods:** This study included 283 N2-3 stage NPC patients with CNN and extracapsular spread who were treated with concurrent chemoradiotherapy. The prescribed doses delivered to the planning target volumes (PTVs), PTVnx, PTVnd, PTV1, and PTV2, were 68–72, 66–70, 60–64, and 52–56 Gy, respectively, in 30–32 fractions. All patients received induction chemotherapy followed by concurrent chemoradiotherapy with cisplatin alone (80–100 mg/m<sup>2</sup>, day 1, every 21 days is a cycle). Two weeks after completion of concurrent chemoradiotherapy, oral capecitabine (twice daily after meals for 14 consecutive days every 3 weeks) was administered to maintenance chemotherapy patients. Maintenance chemotherapy was administered for 6 months.

**Results:** The 5-year overall survival (OS), local relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) rates were 84.8%, 95.4%, and 86.6%, respectively, for all patients. The 5-year OS rates for patients who accepted capecitabine maintenance chemotherapy (group 1) and patients without maintenance chemotherapy (group 2) were 93.8% and 82.1% ( $P=0.021$ ), respectively. The 5-year LRFS rates for groups 1 and 2 were 96.9% and 95.0% ( $P=0.467$ ), respectively. The 5-year DMFS rates for groups 1 and 2 were 93.8% and 84.4% ( $P=0.044$ ), respectively. Hand-Foot syndrome, myelotoxic effects, fatigue, and gastrointestinal symptoms were the common but not severe (grades 1–2) toxicities of the capecitabine maintenance chemotherapy.

**Conclusion:** Capecitabine maintenance chemotherapy improves the outcome and reduces the occurrence of distant failure in N2-3 stage NPC patients with CNN and extracapsular spread. The side effects of treatment were generally tolerated. More clinical trials are required to evaluate the efficacy and toxicity of it.

## Introduction

More than 120,000 cases of nasopharyngeal carcinoma (NPC) were newly diagnosed in 2018, with > 70,000 resulting in death. NPC is a unique carcinoma with racial and geographic variation; southwest China has the highest incidence worldwide.<sup>1</sup> Patients with NPC are asymptomatic for a long time, and up to 85% have lymph node metastases at the time of diagnosis.<sup>2–3</sup> Cervical node necrosis (CNN) and extracapsular spread (ECS), the incidence of which is 22.5–42.1% in patients with NPC, have previously been reported as a strong, independent negative prognostic factor for overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS).<sup>4–5</sup> Given the poor prognosis, it is important to find effective strategies to improve the survival outcomes of this specific sub-group of NPC patients.

NPC is a radiosensitive malignancy. Radiotherapy forms the basis of all treatment stages, and distant metastases are the main reason for treatment failure.<sup>6–7</sup> Many scholars are of the opinion that chemotherapy intensity should be increased to improve patients' outcomes.<sup>8–9</sup> Nevertheless, the role of maintenance chemotherapy is controversial and increases the complication rate.

In recent years, oral 5-FU has been shown to yield very satisfactory results in multiple solid tumors.<sup>10–11</sup> Stockler<sup>12</sup> and Simkens<sup>13</sup> concluded that oral capecitabine is safe and effective, and maintenance treatments with capecitabine are particularly suitable for the overall management of advanced breast and metastatic colorectal cancers. Capecitabine is an oral anticancer fluorouracil derivative that can be converted to 5-FU in vivo. The metronomic use of capecitabine may also be a good choice for NPC, considering its low toxicity and high efficacy.

The aim of the current study was to determine whether N2-3 stage NPC with a CNN and ECS treatment is optimized by concurrent chemoradiotherapy plus capecitabine maintenance chemotherapy.

## Material And Methods

### Patients

Between 1 January 2009 and 30 December 2015, a total of 283 patients with NPC (N2-3) and CNN and ECS were enrolled in the present study.

### *Pretreatment evaluation*

The essential pretreatment assessments included complete medical histories, physical examinations, nasopharyngeal fiberoptic endoscopies, magnetic resonance imaging (MRI) scans of the head and neck, chest radiographies or CTs, abdominal region ultrasonographies or CTs, bone emission CT scans, hematological and biochemical profiles, and dental evaluations. All of the patients were required to provide written informed consents.

### *Intensity-modulated radiation therapy*

Computed tomography contrast-enhanced scanning was applied from the skull cap to 2 cm below the clavicle, with a layer thickness of 3 mm. Under the guidance of Report 50 and Report 62 of the International Commission on Radiation Units and Measurements, the gross tumor volume (GTV)<sub>nx</sub> and GTV<sub>nd</sub> included the entire macroscopic tumor defined after a correlative analysis by the CT and MRI scans. For the clinical target, the high-risk clinical target volume (CTV1) was defined as the nasopharynx GTV plus a 5–10 mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) that can encompass the high-risk sites of microscopic extension and the whole nasopharynx. The low-risk CTV2 was defined as the nasopharynx GTV plus a 5–10 mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) that can encompass the low-risk sites of microscopic extension, including the skull base, clivus, sphenoid sinus, parapharyngeal space, pterygoid fossae, posterior parts of the nasal

cavity, pterygopalatine fossae, retropharyngeal nodal regions, and cervical node levels II, III, IV, and V. The total doses were prescribed to the median of the target volume, and the 95% isodose was approximately similar to the planning target volume (PTV). PTVnx, PTVnd, PTV1, and PTV2 were generated by adding 5mm margins to GTVnx, GTVnd, CTV1, and CTV2, respectively. The prescribed doses delivered to PTVnx, PTVnd, PTV1, and PTV2 were 68–72, 66–70, 60–64, and 52–56 Gy, respectively, in 30–32 fractions.

### ***Magnetic resonance imaging diagnostic criteria***

On a MRI, the CNN is seen as a focal area of high signal intensity on T2-weighted images and as an area of low signal intensity on contrast material–enhanced T1-weighted images—with or without a surrounding rim of enhancement<sup>14–16</sup> (Fig. 1).

ECS is defined as the presence of indistinct nodal margins, irregular nodal capsular enhancements, or the infiltration of surrounding fats or muscle planes or fusions with adjacent LNs<sup>17</sup> (Fig.1).

### ***Chemotherapy***

All patients underwent induction chemotherapy followed by concurrent chemoradiotherapy with cisplatin alone (80–100 mg/m<sup>2</sup>, day 1, every 21 days is a cycle).

Two weeks after the completion of concurrent chemoradiotherapy, oral capecitabine (twice daily after meals for 14 consecutive days every 3 weeks) was administered to maintenance chemotherapy patients. The dose of capecitabine was determined on the basis of the body surface area [1250 mg/m<sup>2</sup> twice per day]. Maintenance chemotherapy was administered for 6 months or terminated if there was disease progression or intolerable toxicity. The dose of capecitabine was modified according to the toxicity profile. The chemotherapy was not delayed or paused until the nadir values were  $\geq$ 1,500 cells/ $\mu$ L for neutrophils and  $\geq$ 100,000 cells/ $\mu$ L for platelets.

### ***Follow-up***

During the treatment, all patients underwent weekly examinations. Then, the patients were evaluated for tumor responses through nasopharyngeal fiberoptic endoscopy and MRI. Toxicities were observed and noted according to the Toxicity Criteria of the Radiation Therapy Oncology Group. Efficacy was determined using the RECIST solid tumor efficacy evaluation criteria.

Subsequently, the patients were followed up every 3 months during the first 2 years, every 6 months for the third year, and every 1 year thereafter. Each follow-up included a physical examination, nasopharyngeal fiberoptic endoscopy, chest radiography or CT, abdominal region ultrasonography or CT, and a hematological and biochemical profile. The MRI scan was performed every 6 months.

Additional CT and bone emission CT scans were performed to confirm any suspicious lesions for distant metastasis.

## **Statistical analysis**

The data was processed using SPSS 23.0 software. The OS was calculated from the date of diagnosis until death or the last follow-up using the Kaplan–Meier method, and the difference was analyzed using a two-sided log-rank test. The local relapse-free survival (LRFS) and DMFS were defined as the time from the day of diagnosis to the locoregional progression and distant metastasis, respectively. The LRFS and DMFS were also calculated and constructed using the Kaplan–Meier method. A comparison between the groups for the frequency of data was carried out using the  $\chi^2$ -test. P-values  $<0.05$  were considered statistically significant.

## **Results**

### **Patient demographics**

The male-to-female ratio was 209:74. All patients were WHO II with respect to histologic classification. Sixty-five patients (23.0%) accepted the capecitabine maintenance chemotherapy. The clinical characteristics of the 283 NPC patients are listed in Table 1.

### **OS**

The 5-year OS was 84.8% for all patients. Forty-three patients died (distant metastasis, 31; locoregional recurrence, 11; and unknown cause, 1).

The 5-year OS rates for the patients who accepted capecitabine maintenance chemotherapy (group 1) and patients who did not accept maintenance chemotherapy (group 2) were 93.8% and 82.1% ( $P=0.021$ , Figure 2), respectively.

### **Local relapse-free survival (LRFS)**

The 5-year LRFS was 95.4%. Thirteen patients exhibited locoregional recurrences. The 5-year LRFS rates for patients who accepted the capecitabine maintenance chemotherapy (group 1) and patients who did not accept the maintenance chemotherapy (group 2) were 96.9% and 95.0%, respectively ( $P=0.467$ , Figure 3).

### **DMFS**

The 5-year DMFS rate was 86.6%. Thirty-eight patients presented distant metastases (lung, 8; bone, 6; liver, 9; brain, 1; soft tissue, 1; and multiple site metastases, 12).

The 5-year DMFS rates for patients who accepted the capecitabine maintenance chemotherapy (group 1) and patients who did not accept the maintenance chemotherapy (group 2) were 93.8% and 84.4%, respectively ( $P=0.044$ , Figure 4).

### **Toxicities of capecitabine maintenance chemotherapy**

Hand-Foot syndrome, myelotoxic effects, fatigue, and gastrointestinal symptoms were the common but not severe (grades 1–2) toxicities of the capecitabine maintenance chemotherapy. No grade 4 toxicity or treatment-related deaths occurred during the capecitabine maintenance chemotherapy; detailed information is covered in Table 2.

## Discussion

NPC is a unique carcinoma with racial and geographical variations; southwest China has the highest incidence of NPC worldwide.<sup>1</sup> NPC is a radiosensitive malignancy. Radiotherapy forms the basis for all treatments in patients with NPC. Intensity-modulated radiation therapy (IMRT) has replaced conventional two-dimensional radiotherapy as the pivotal radiotherapy technique, and it has improved the local control rate to > 90%. Distant metastases are the main treatment failure pattern in patients with NPC.<sup>18–19</sup> Therefore, it is crucial to choose a proper therapeutic modality to maximally reduce distant metastases.

It is unknown if increasing the intensity of chemotherapy will improve the outcome of patients with NPC. Multiple studies have failed to demonstrate a significant advantage in the entire population without risk stratification. Several randomized studies have attempted to elucidate this matter, but they failed to get the expected result.<sup>20–21</sup> In our opinion, the major goal of maintenance chemotherapy in patients with NPC is to reduce the occurrence of distant failure; however, not all NPC patients require maintenance chemotherapy. Of note, none of the studies focused on the ECS and CNN sub-groups. Due to a lack of stratification, we were intent on identifying the specific sub-group that would benefit from maintenance chemotherapy.

CNN and ECS is a late biological event in the evolution of tumor metastases in lymph nodes, and it often occurs at the interface between necrotic areas and well-aerated cells. An increase in the radioresistance of hypoxic tumor cells has been well-documented in previous studies,<sup>22–23</sup> therefore, CNN may serve as a marker for hypoxia. ECS may serve as a marker for an increase in the number of metastases. The presence of CNN and ECS in tumors induces relatively poor sensitivity to radiotherapy or chemotherapy. Moreover, it can lead to gene amplification with a resistance that can increase tumor aggressiveness and accelerate progression.<sup>24–27</sup>

CNN and ECS proved to be an independent negative prognostic factor for OS, DFS, and DMFS.<sup>28–30</sup> It has been reported that an increase in chemotherapy intensity provides survival benefits for high-risk patients.<sup>31–32</sup> Therefore, identifying patients as being high risk is significant for selecting an individualized therapy strategy. Assuming that the last fraction of IMRT is completed, the tumor does not often completely regress, especially in patients with CNN and ECS.<sup>33</sup> Thus, maintenance chemotherapy is an effective method to improve treatment outcomes.

Capecitabine is an oral pro-drug of 5-fluorouracil (5-FU), and it is frequently used for treating cancer. Capecitabine proved to have very satisfactory results in multiple solid tumors.<sup>11–13</sup> It is completely and rapidly absorbed after oral administration.<sup>34–35</sup> It has been concluded that oral capecitabine is safe and

effective, and maintenance treatment with capecitabine is particularly suitable for the overall management of advanced breast cancer.<sup>36–37</sup>

In our study, the 5-year OS, LRFS, and DMFS rates were 84.8%, 95.4%, and 86.6%, respectively. The data is similar to other studies.<sup>28–29</sup> Our data reveals the pattern of treatment failure is distant metastasis. The most common site of metastasis includes the lungs, brain, liver and bones. The 5-year DMFS rates for groups 1 and 2 were 93.8% and 84.4% ( $P = 0.044$ ), respectively. Thus, capecitabine maintenance chemotherapy may improve DMFS rates in N2-3 NPC patients with CNN and ECS. The role of adjuvant chemotherapy is controversial. Our study demonstrates a different conclusion compared to the previous studies. Because the shortcoming was a lack of stratification in the previous studies,<sup>20–21</sup> we were intent on identifying the specific sub-group that would benefit from maintenance chemotherapy.

Based on our sub-group analysis, 166 patients had MRI scans of the head and neck immediately when concurrent chemoradiotherapy was completed. There were only 38 patients who had complete responses; the remaining patients had partial responses. We will choose to observe and evaluate these 3 months later. With time, the residual tumors became disintegrated and fully disappeared by 3 months' time. Our studies failed to demonstrate a significant relationship between the patients with PR and CR. The number of cases was too small to analyze statistically, a larger sample size is needed to verify this.

Two of the major constraints for maintenance chemotherapy are toxicity and tolerability. The major toxicities encountered included manageable myelosuppression, oral mucositis, and radiation dermatitis after CCRT. Patients can tolerate an oral chemotherapy within two weeks after CCRT. Hand-Foot syndrome ( $n = 52,80\%$ ), leucopenia ( $n = 45,69.2\%$ ), anemia ( $n = 41,63.1\%$ ), fatigue ( $n = 49,75.4\%$ ), and nausea ( $n = 39,60.0\%$ ) were the common but not severe symptoms (grades 1–2) during maintenance chemotherapy.

We proposed a new idea for selecting a better individualized therapy to maximally reduce distant metastases. Nevertheless, there were some limitations in this study. Specifically, the study had a retrospective design and some existent biases. Additional studies with a larger sample size and unit participation are imperative.

## Conclusion

In this study we showed that capecitabine maintenance chemotherapy can improve the outcomes of and reduce the occurrence of distant failures in N2-3 stage NPC patients with CNN and ECS.

## List Of Abbreviations

NPC:nasopharyngeal carcinoma; CNN:cervical node necrosis; ECS:extracapsular spread; PTVs:planning target volumes; OS:overall survival; LRFS:local relapse-free survival; DMFS: distant metastasis-free survival; MRI:magnetic resonance imaging; GTV:the gross tumor volume; CTV: clinical target volume;

# **Declarations**

## **1. Ethics approval and consent to participate**

This study was reviewed and approved by the Ethics Committee of LiuZhou People's Hospital, GuangXi, China.() Written informed consent was obtained from each patient. this study was conducted in accordance with the Declaration of Helsinki.

## **2. Consent for publication**

Not applicable.

## **3. Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

## **4. Competing interests**

The authors declare that they have no competing interests.

## **5. Funding**

None.

## **6. Authors' contributions**

Tingliu and Siwen liu conceived and designed the study. Yuting Gu and Xuehua Wen collected, analyzed, and interpreted the data, prepared the draft and gave final approval of the version to be submitted. Tingliu and Siwen liu undertook data analysis and interpretation, and performed the statistical analysis. All authors approved the final manuscript.

## **7. Acknowledgements**

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## Tables

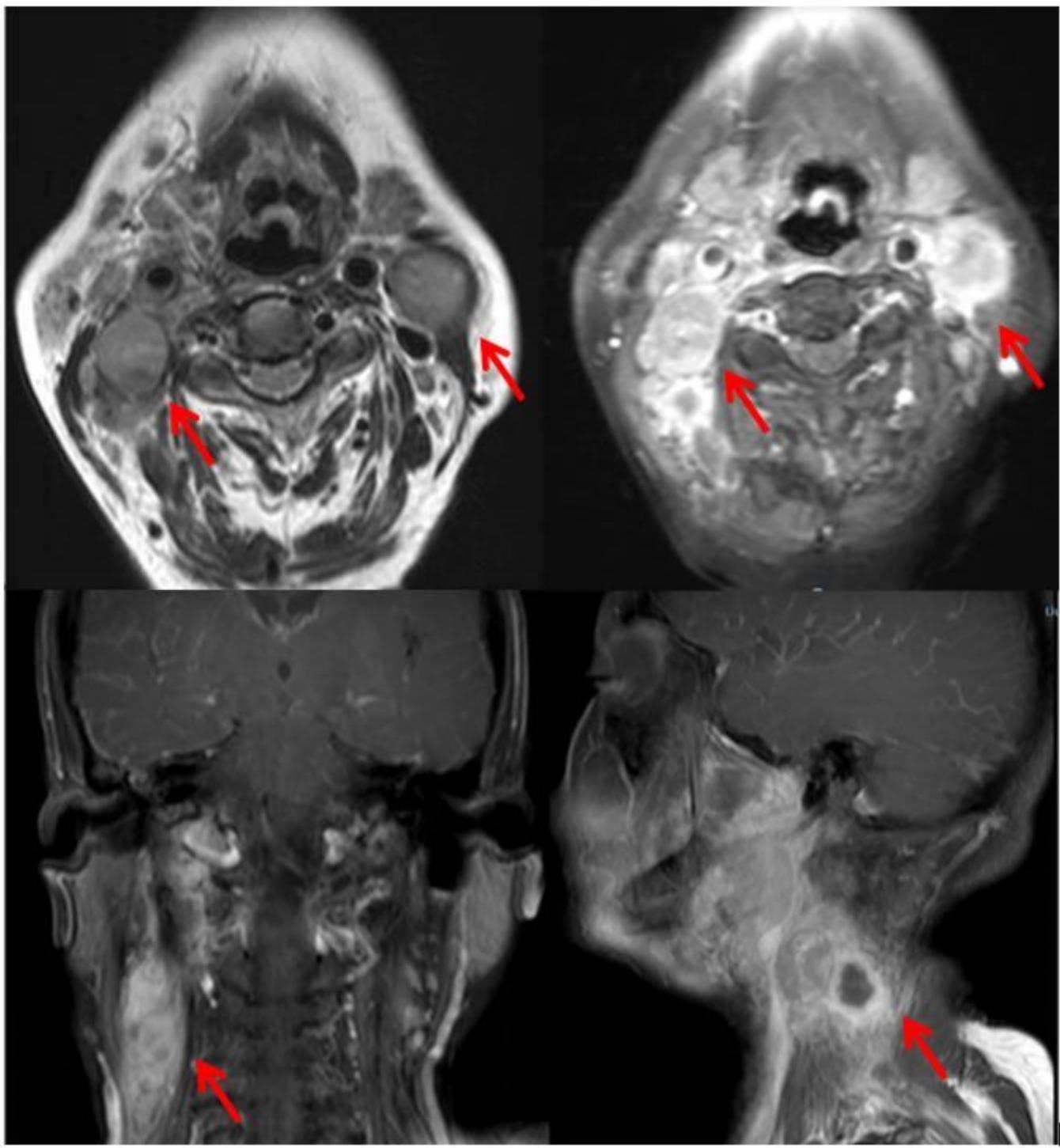
Table 1  
Clinical characteristics of patients

<b>Characteristic</b>	<b>CCRT-MC Patients(n = 65)</b>	<b>CCRT-non-MC Patients(n = 218)</b>
Age (years)		
Median	45	47
Range	30–69	20–72
Gender, n (%)		
Male	51(78.4)	158(72.4)
Female	14(21.5)	60(27.5)
Histology		
WHO II	65	218
T stage, n (%)		
T1	1(1.5)	5(2.2)
T2	12(18.4)	41(18.8)
T3	24(36.9)	96(44.0)
T4	28(43.0)	76(34.8)
N stage, n (%)		
N2	48(73.8)	147(67.4)
N3	17(26.1)	71(32.5)
UICC stage		
III	28(43.0)	103(47.2)
IV	37(56.9)	115(52.7)
NeoCT (cycles), n (%)		
1	0	1(0.4)
2	53(82.8)	187(85.3)
3	11(17.1)	31(14.3)
post-CCRT MRI response, n		
CR	9	29
PR	36	92

Table 2  
Adverse events during maintenance chemotherapy(n = 65).

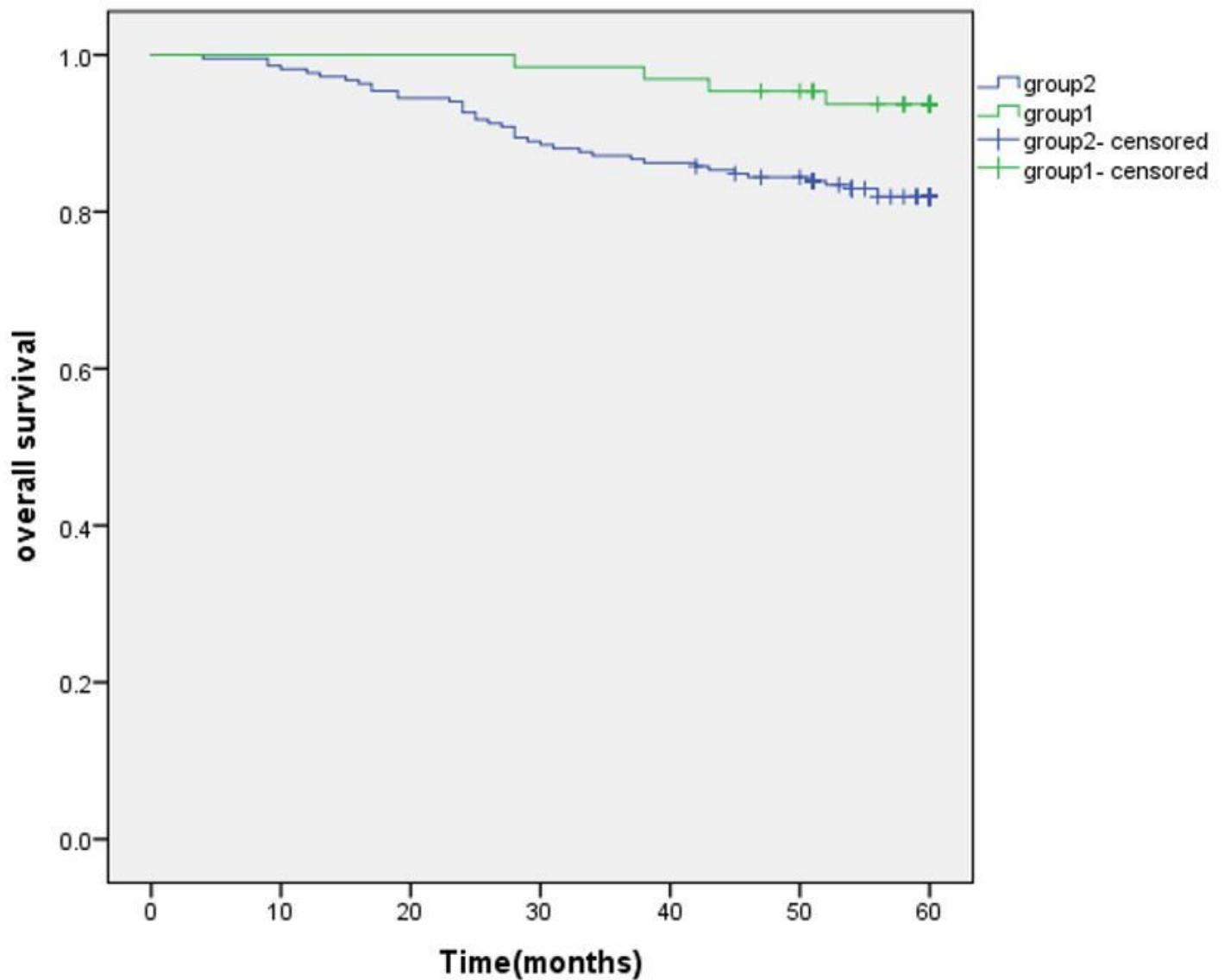
Toxicity	Grade 1		Grade 2		Grade 3	
	n	%	n	%	n	%
Hand-Foot syndrome	36	55.4	16	24.6	0	0
myelotoxic effects						
Leucopenia	38	58.4	7	10.8	0	0
Anemia	34	52.3	7	10.8	1	1.5
Thrombocytopenia	11	16.9	0	0	0	0
fatigue	47	72.3	2	3.1	0	0
gastrointestinal symptoms						
Nausea	35	53.8	4	6.2	0	0
Vomiting	7	10.8	0	0	0	0
Diarrhea	4	6.2	0	0	0	0
Hepatotoxicity	2	3.1	0	0	0	0

## Figures



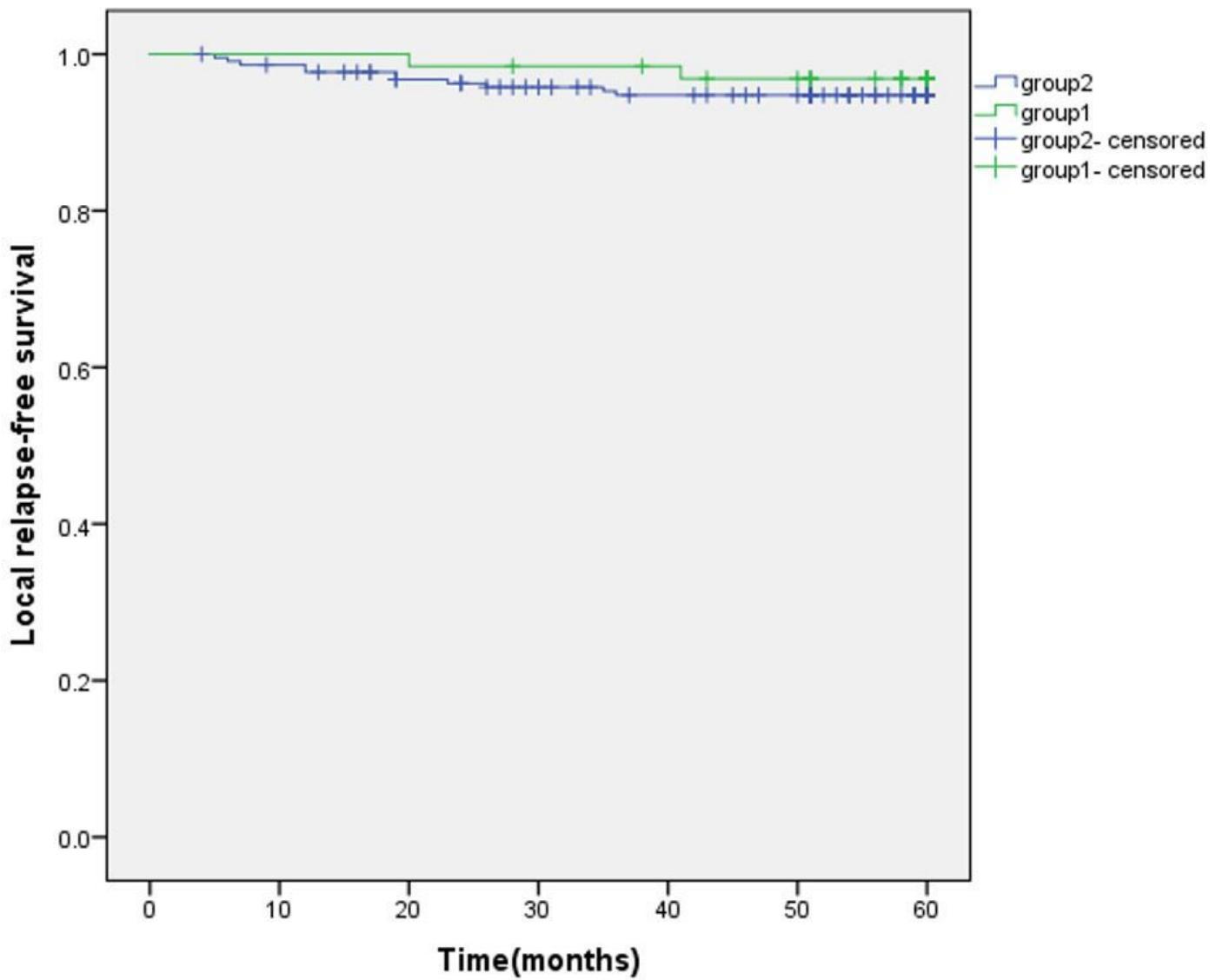
**Figure 1**

Representative MRI photographs of CNN and ECS



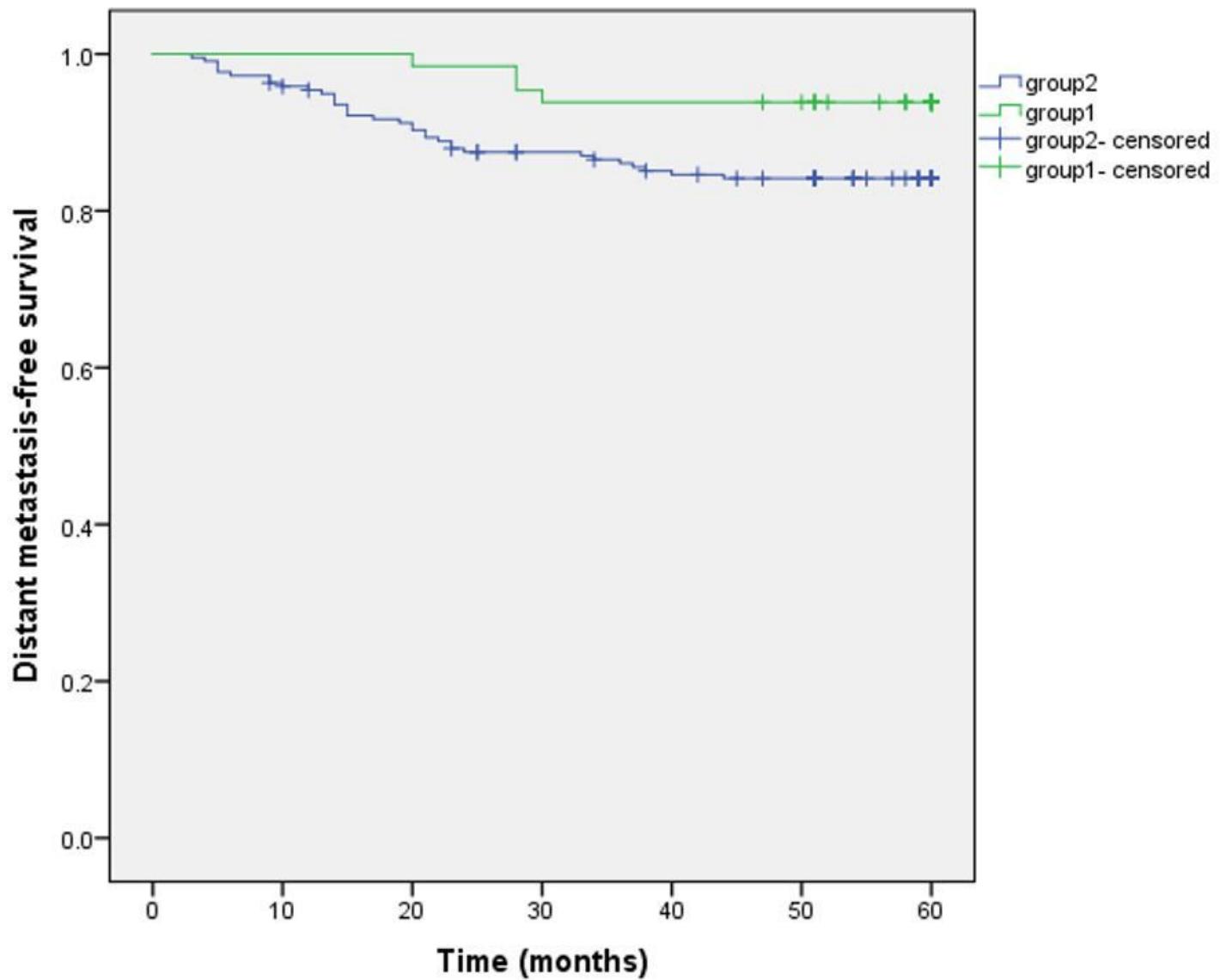
**Figure 2**

Kaplan-Meier estimate of overall survival for patients who accepted capecitabine maintenance chemotherapy (group 1) and patients who did not accept maintenance chemotherapy (group 2).



**Figure 3**

Kaplan-Meier estimate of LRFS for patients who accepted capecitabine maintenance chemotherapy (group 1) and patients who did not accept maintenance chemotherapy (group 2).



**Figure 4**

Kaplan-Meier estimate of DMFS for patients who accepted capecitabine maintenance chemotherapy (group 1) and patients who did not accept maintenance chemotherapy (group 2).