Laparoscopic microwave ablation in patients with hepatocellular carcinoma: a prospective cohort study

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Abstract

Objectives: There are no prospective studies of laparoscopic microwave (MW) ablation in patients with hepatocellular carcinoma (HCC). The aim of this study was to demonstrate the safety and efficacy of laparoscopic MW ablation.

Methods: A prospective study group of consecutive HCC patients considered ineligible for liver resection and/or percutaneous ablation was conducted from December 2009 to December 2010. Short-term (3-month) outcomes included a centralized revision of radiological response, mortality and morbidity. Mid-term (24-month) outcomes included time to recurrence in the study group compared with that in a cohort of consecutive patients treated with laparoscopic radiofrequency (RF) ablation using propensity score analysis.

Results: A total of 42 patients were enrolled. Their median age was 64 years; 67% were positive for hepatitis C virus; 33% were of Child–Pugh class B status; the median tumour diameter was 2.5 cm, and 48% of patients had multinodular HCC. In 47 of 50 (94%) nodules treated with MW ablation, a complete radiological response was observed at 3 months. There was no perioperative mortality. The overall morbidity rate was 24%. The 2-year survival rate was 79% and the 2-year recurrence rate was 55%. Using propensity score analysis (in 28 MW ablation patients and 28 RF ablation controls), 2-year recurrence rates were 55% in the MW ablation group and 77% in the control group (P = 0.03).

Conclusions: Laparoscopic MW ablation is a safe and effective therapeutic option for selected HCC patients who are ineligible for liver resection and/or percutaneous ablation.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world.¹

The prognosis in HCC is very poor because of the high degree of malignancy, high recurrence rates and the impaired liver function associated with the disease.

Liver transplantation (LT) is the only option able to facilitate the cure of both the tumour and the underlying chronic liver disease, but the severe shortage of donor organs greatly limits its applicability. Surgical resection is considered the treatment of choice for HCC in patients with and without cirrhosis, provided that liver function reserve is adequate.²

Unfortunately, the majority of patients (75%) with HCC are not candidates for resection, firstly because of their poor hepatic functional reserve, and secondly because advanced tumours, a tumour location close to major intrahepatic vessels and multifocal tumours preclude a negative margin resection.³

Because of the limited applicability of surgical treatment for HCC, over the past decade non-surgical therapeutic modalities...
have been developed, such as transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), and percutaneous radiofrequency (RF) and microwave (MW) ablation.\(^5\,\text{,}\,^6\)

Although both thermal ablation therapies (RF and MW) have been widely used for the local treatment of HCC, the differences between these two techniques have not been clearly demonstrated.\(^5\) Radiofrequency ablation is considered the first option in the treatment of HCC of ≤2.0 cm, although MW ablation seems to have some advantages.\(^6\,\text{,}\,^7\) In particular, MW ablation potentially induces tumour necrosis within a shorter period of ablation, does not result in tissue desiccation or charring and achieves a greater zone of intra-tumoral thermal injury.\(^6\) Randomized controlled trials and multicentre studies comparing RF and MW ablation have been performed in recent decades, but no differences in effects on survival or local recurrence were observed.\(^5\,\text{,}\,^8\,\text{–}\,^10\) This, together with the lower cost and a reduced complexity of use associated with RF ablation accounts for the prevailing use of this method until 2009, when a new MW probe was introduced. Microwave ablation is affected by the phenomenon of ‘back heating’ and exhibits a teardrop-shaped heating pattern as a result of both poor control over the power reflected (the portion of MW power unabsorbed by the tissue and propagating back along the antenna shaft) and severe losses of power along the antenna feeding cable. In 2009 a new probe was designed, in which miniaturized cap-chokes were applied in the MW antenna to minimize the teardrop-shaped ablation zone and to obtain more defined areas of necrosis. An integrated cooling system was also added to prevent the shaft from overheating.\(^11\)

Although recent evidence shows that MW ablation has a good safety and efficacy profile for HCC of >2.0 cm,\(^12\,\text{–}\,^15\) until now no prospective studies have evaluated this new technology in comparison with RF ablation in a laparoscopy-only setting.

A laparoscopic approach to the ablation of HCC is viable in a significant proportion of patients who are judged to be unsuitable for hepatic resection or percutaneous ablation because of impaired liver function, tumour location or extension, or concurrent clinical conditions. Moreover, a laparoscopic approach facilitates the treatment of several lesions during the same session, including with different ablation techniques.\(^10\,\text{,}\,^16\)

This paper reports a prospective study conducted to assess the efficacy of laparoscopic MW ablation in patients with HCC who are ineligible for resection and percutaneous ablation.

### Materials and methods

#### Patients

Consecutive patients with HCC and cirrhosis evaluated at the Hepatobiliary Surgery and Liver Transplantation Unit at Padua University Hospital between December 2009 and December 2010 were treated according to a previously described\(^10\) algorithm in which laparoscopic MW ablation was considered as a first-line therapy for patients with Barcelona Clinic Liver Cancer (BCLC) class A disease and super-selected patients with BCLC class B disease who were judged ineligible for liver resection and/or percutaneous ablation as a result of negative prognostic factors or technical contraindications. The selection criteria for laparoscopic ablation (LA) are described in detail in Table 1. The policy of the study institution decrees that LT in HCC patients with BCLC class A or B disease is used only as a second-line or salvage therapy.\(^17\,\text{–}\,^18\)

In all of the patients enrolled, the diagnosis of HCC was based on American Association for the Study of Liver Diseases criteria for liver resection were generally followed when tumour location or extension required a major hepatectomy (resection of more than two liver segments). In selected cases major liver resection was performed in HCC patients who did fulfil guidelines using technical expedients such as a portocaval shunt. The same strategy was followed for patients with MELD scores of >10.\(^1\)

In selected HCC patients with Child–Pugh class C cirrhosis waiting for liver transplantation, laparoscopic ablation was considered as bridging therapy; these patients were not included in this study. BCLC, Barcelona Clinic Liver Cancer; MELD, Model for End-stage Liver Disease; GI, gastrointestinal; PT, prothrombin time.

### Table 1

| Selection criteria for laparoscopic microwave ablation in hepatocellular carcinoma (HCC) patients at Padua University Hospital |
|-----------------|------------------|
| **Inclusion criteria** | **Patients, n (%)** |
| **Ineligibility for liver resection** | |
| • Major resection in BCLC A2-A3-A4 disease\(^a\) | 18 (43%) |
| • Technical contraindications | 9 (20%) |
| • Major resection in patients with MELD score of >10\(^a\) | 15 (37%) |
| **Ineligibility for percutaneous ablation** | |
| • Critical location (proximity to GI tract or bladder or major hepatic vessels; superficial or exophytic nodules) | 29 (69%) |
| • Untreatable ascites | 4 (11%) |
| • Severe coagulopathy (PT of <40% and/or platelet count of <30 × 10\(^9\)) | 9 (20%) |
| **Exclusion criteria** | |
| **Severe liver decompensation** | |
| • MELD score of >20 | 0 |
| • Child–Pugh class C\(^6\) | 0 |
| **Large multinodular HCC** | |
| • Nodule size of >7.0 cm | 0 |
| • Number of nodules >5 | 0 |

*American Association for the Study of Liver Diseases criteria for liver resection were generally followed when tumour location or extension required a major hepatectomy (resection of more than two liver segments). In selected cases major liver resection was performed in HCC patients who did fulfill guidelines using technical expedients such as a portocaval shunt. The same strategy was followed for patients with MELD scores of >10.\(^1\)

\(^\text{a}\)In selected HCC patients with Child–Pugh class C cirrhosis waiting for liver transplantation, laparoscopic ablation was considered as bridging therapy; these patients were not included in this study.
Surgical procedure and postoperative follow-up

Procedures were performed with the patient in a supine position in all cases. The open approach (Hasson’s technique) was used to obtain a pneumoperitoneum and inflation pressure was maintained at 8–12 mmHg. A second trocar was inserted in the right or left upper quadrant (for right or left liver lesions, respectively, and according to liver anatomy) to allow the passage of the ultrasound probe. After the peritoneal cavity had been explored, laparoscopic intraoperative ultrasound was performed to complete the disease staging, confirm the location of the tumour and establish its relationship with the major hepatic vasculature.

The ablation technique adopted in the study group was MW ablation (AMICA; HS Hospital Service SpA, Aprilia, Italy). In the retrospective control group, RF ablation was used (Cool-tip RF; Valleylab-Tyco Healthcare Group, Boulder, CO, USA).

Microwave and RF ablation were mandatory only for nodules of >1.0 cm. Nodules of <1.0 cm detected during laparoscopic ultrasound could be treated by alcohol injection (5–20 ml) according to the surgeon’s decision.

Ablation needles were inserted percutaneously and placed inside the lesion under laparoscopic ultrasound guidance. A small tubular drain was then inserted to be removed postoperatively.

The local efficacy of ablation at the study institution was evaluated with CT and/or MRI in all patients at 20–40 days after LA and at 3 months following modified RECIST (response evaluation criteria in solid tumours) recommendations. All radiological examinations were submitted to centralized radiological revision by one expert radiologist and fulfilled specific technical requirements: multi-slice CT scanners (typically of 8–64 detectors) were used for dynamic acquisition in the three phases for the study of hepatic parenchyma (arterial, portal, equilibrium) after an infusion of iodinated contrast media of 320–400 mg/ml at a rate of 2–4 ml/s, using a bolus tracking technique.

Magnetic resonance imaging scans were obtained as multiplanar T2-weighted, T2-weighted with fat saturation, T1-weighted out of phase and in phase acquisitions after injection of paramagnetic contrast agent (0.1–0.2 mmol/kg at 2 ml/s) during exposure to a highly magnetic field (1.0–1.5 TESLA).

In the case of complete ablation, an enhanced follow-up protocol consisting of CT and/or MRI repeated every 3 months for the first year and every 6 months thereafter was followed.

Incomplete ablation or local recurrences were treated according to the study institution’s treatment algorithm. In this context, the more common therapies were a repeat LA procedure, TACE and LT.

Study design

The objective of this study was to evaluate the efficacy and safety of laparoscopic MW ablation in HCC patients who were judged to be unsuitable for liver resection or percutaneous ablation, but who fulfilled the study inclusion criteria (Table 1).

The primary endpoint was the number of patients free of local tumour persistence or progression [partial, stable or progressive disease according to modified RECIST (mRECIST) criteria] assessed at 3 months after the procedure. Secondary endpoints were: postoperative mortality and morbidity; recurrence rate at 24 months, and patient survival at 24 months.

The planned enrolment period was 12 months. The minimal follow-up required in each enrolled patient was 24 months.

This study was designed as a classical one-stage Phase II trial with the following assumptions: the hypotheses of interest were $H_0: r \leq 50\%$ against $H_1: r \geq 75\%$, where $r$ is the proportion of patients free of local progression at 3 months after the procedure; the type I error rate was set at 5%, and the type II error rate was set at 10%.

Under these assumptions, a minimum of 33 patients were required. The evaluation of treatment efficacy was based on the number of patients free of local progression at 3 months after the procedure: if this number was at most 21, the treatment would be declared insufficiently effective; if this number amounted to 22 or more, the treatment would be declared sufficiently effective.

Patients who were lost from follow-up within 3 months were to be replaced in order to ensure that 33 patients were evaluable at 3 months.

A total of 100 consecutive HCC patients treated with laparoscopic RF ablation during the period 2004–2009 were selected from the study institution’s prospective HCC database using the same criteria described in Table 1. These patients were used to represent an historical control group to test the mid-term efficacy of laparoscopic MW ablation (recurrence rate and patient survival at 24 months). In order to limit selection bias in this retrospective cohort, the first 30 cases of LA performed at the study institution were excluded and a propensity score analysis was performed.

Statistical analysis

Values for continuous variables are presented as medians (ranges). Values for categorical-nominal variables are presented as frequencies (%). For subgroup comparisons, quantitative variables were compared using Student’s t-test or the Wilcoxon rank sum test, and categorical variables were compared using the chi-squared or Fisher’s exact test, as appropriate.

The length of the follow-up after LA was calculated from the date of the operation to the date of HCC recurrence (for time-to-recurrence analysis) or the patient’s death (for survival analysis) or the latest follow-up. For both recurrence and survival analysis, LT represented a censor point. The last follow-up date considered was 15 March 2013. The length of follow-up and survival were expressed as the median (range).

Time-to-recurrence and overall survival curves were calculated using the Kaplan–Meier technique and compared with the log-rank test.

To overcome biases arising from the different distributions of covariates among patients undergoing MW ablation and those undergoing RF ablation, a one-to-one match was created using
propensity score analysis. Given the matched nature of the analysis, differences in continuous baseline variables were assessed using the paired t-test. A P-value of <0.05 was considered to indicate statistical significance.

All statistical calculations were performed using JMP Version 9.0 2010 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics

Laparoscopic ablation was prospectively applied in 42 consecutive HCC patients between December 2009 and December 2010. The characteristics of these patients are shown in Table 2. The median patient age was 64 years and the sample showed a male predominance. The main aetiology of cirrhosis was hepatitis C virus infection (67%), followed by alcohol abuse (28%). The median MELD score was 10 and 33% of patients were of Child–Pugh class B status.

Only 10 patients (24%) had very early-stage HCC, whereas nine (21%) demonstrated BCLC stage B disease. The reasons why patients were considered ineligible for resection and percutaneous ablation are depicted in Table 1.

A total of 72 nodules were treated during the laparoscopic procedure in the 42 enrolled patients: 50 of these nodules were ablated using MW devices, and 22 nodules that were <1.0 cm in size underwent alcohol injection as established by the study protocol.

Short-term analysis

Blood transfusions were given to two patients (5%). The conversion rate during LA was 0%.

There was no perioperative mortality. The overall morbidity rate was 24% (Table S1, online). The most common postoperative complication was fever, which occurred in five patients (12%).

The median postoperative hospital stay was 3 days (range: 1–8 days).

Imaging studies at 3 months showed incomplete ablation in only three (6%) of the 50 nodules (Table S2, online). Complete ablation was achieved in 100% of nodules of <3.0 cm and in 80% of those of >3.0 cm in size (Tables S3 and S4, online).

In a patient-by-patient analysis, 37 patients (88%) were found to be free of local recurrence at 3 months, a finding that marked the achievement of the primary endpoint of the study.

Mid-term analysis

The characteristics of the prospective cohort of 42 patients treated with MW ablation were compared with those of a retrospective cohort of 100 consecutive patients submitted to RF ablation during 2004–2009. The two study populations were extremely similar (Table 3) because the same selection criteria for LA were applied in both (Table 1).

Nevertheless, significant differences between the study and control groups in the aetiology of underlying liver disease and in α-fetoprotein values were found (Table 3).

When a 24-month follow-up period was applied in both the (unmatched) cohorts, 2-year survival rates were 81% and 59%, respectively, in the MW and RF groups (P = 0.0089) (Fig. 1).

Two-year recurrence rates were 55% in MW patients and 74% in RF patients (P = 0.0162) (Fig. 2).

To simulate a randomized clinical trial involving two comparable cohorts of patients, a propensity score analysis was performed. This method provided two subgroups of 28 patients each without significant differences in the covariates analysed (Table 3).

The two matched cohorts demonstrated similar rates of survival (P = 0.2056) (Fig. 3). Conversely, MW patients maintained a better recurrence profile than those submitted to RF ablation: 2-year recurrence rates were 55% and 77% in the MW and RF groups, respectively (P = 0.0354) (Fig. 4).
Discussion

Although MW ablation theoretically has greater potential ablation power than RF ablation, there are no studies demonstrating the superiority of MW over RF ablation.6,8,10 This is the first prospective study to evaluate the safety and efficacy of the new MW setting in a laparoscopic-only approach in HCC patients. Although several recent experiences12–15 have demonstrated the safety and efficacy of MW ablation in larger numbers of patients, these series were retrospective, often considered other liver tumours in addition to HCC, did not focus on a laparoscopic approach, and reported incomplete data, or non-uniform selection criteria or follow-up schedules, as is typical of retrospective studies.

Table 3 Comparisons between patients with hepatocellular carcinoma undergoing laparoscopic microwave (MW) ablation and those undergoing laparoscopic radiofrequency (RF) ablation (unmatched and matched cohorts)

<table>
<thead>
<tr>
<th>Variables</th>
<th>MW ablation unmatched patients (n = 42)</th>
<th>RF ablation unmatched patients (n = 100)</th>
<th>MW ablation matched patients (n = 28)</th>
<th>RF ablation matched patients (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>7 (17%)</td>
<td>17 (17%)</td>
<td>5 (18%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>64 (47–81)</td>
<td>63 (34–81)</td>
<td>64 (47–80)</td>
<td>64 (34–80)</td>
</tr>
<tr>
<td>Aetiology of liver cirrhosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV-related</td>
<td>28 (67%)</td>
<td>39 (39%)a</td>
<td>16 (57%)</td>
<td>16 (57%)</td>
</tr>
<tr>
<td>HBV-related</td>
<td>2 (5%)</td>
<td>28 (28%)b</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Alcohol-related</td>
<td>12 (29%)</td>
<td>40 (40%)</td>
<td>10 (36%)</td>
<td>10 (36%)</td>
</tr>
<tr>
<td>Child–Pugh score, median (range)</td>
<td>6 (5–9)</td>
<td>6 (5–9)</td>
<td>6 (5–8)</td>
<td>6 (5–9)</td>
</tr>
<tr>
<td>MELD score, median (range)</td>
<td>10 (6–16)</td>
<td>10 (6–19)</td>
<td>11 (6–16)</td>
<td>10 (7–19)</td>
</tr>
<tr>
<td>α-fetoprotein, ng/ml, median (range)</td>
<td>7 (2–775)</td>
<td>44 (1–28356)b</td>
<td>9 (2–775)</td>
<td>8 (1–148)</td>
</tr>
<tr>
<td>Largest nodule diameter, mm, median (range)</td>
<td>25 (15–53)</td>
<td>30 (10–60)</td>
<td>25 (15–53)</td>
<td>27 (12–60)</td>
</tr>
<tr>
<td>Number of nodules, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (52%)</td>
<td>54 (54%)</td>
<td>12 (43%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>18 (43%)</td>
<td>39 (39%)</td>
<td>15 (54%)</td>
<td>12 (43%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>2 (5%)</td>
<td>7 (7%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>BCLC stage B disease, n (%)</td>
<td>9 (21%)</td>
<td>29 (29%)</td>
<td>7 (25%)</td>
<td>7 (25%)</td>
</tr>
</tbody>
</table>

aP < 0.05;
bP < 0.1.
HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, Model for End-stage Liver Disease; BCLC, Barcelona Clinic Liver Cancer.

Figure 1 Kaplan–Meier curves showing survival in unmatched cohorts of hepatocellular carcinoma patients submitted to laparoscopic microwave (MW) or radiofrequency (RF) ablation (log-rank test, P = 0.0089)

Figure 2 Kaplan–Meier curves showing recurrence in unmatched cohorts of hepatocellular carcinoma patients submitted to laparoscopic microwave (MW) or radiofrequency (RF) ablation (log-rank test, P = 0.0162)
This study was designed in 2009 to evaluate short-term outcomes in patients undergoing laparoscopic MW ablation. The laparoscopic approach was already in frequent use at the study institution and represented the ideal setting in which to test this new MW technology because it has greater intrinsic ability to avoid the occurrence of side-effects such as bleeding or damage to extrahepatic organs that are close to the HCC. In the 12-month enrolment period, the number of patients recruited ($n = 42$) exceeded that required according to sample size calculations ($n = 33$).

This study is supported by its substantial recruitment numbers and the fact that its primary endpoint was achieved.

The present results broadly overlap with those of other study groups that have used laparoscopic RF ablation, particularly with reference to the safety of the procedure: the present study found no perioperative mortality and a low incidence of specific morbidity (24%), both of which are comparable with findings elsewhere. The surgical conversion rate in the present study (0%) is also in line with rates reported in the literature. The median postoperative hospital stay in the present study was also relatively short (3 days) and similar to those reported elsewhere.

In other experiences, LA was used in patients who were eligible for traditional treatments and who were selected according to the numbers and sizes of nodules and the severity of cirrhosis. The present study’s enrolment criteria were particular in that LA was applied prospectively to super-selected patients who were considered unresectable or ineligible for percutaneous ablation (Table 1).

This particular feature of the treatment algorithm used in the present study derives from a hierarchy of therapeutic options, in which a potentially radical therapy can be assigned regardless of BCLC stage whenever possible: the first option is to consider liver resection or percutaneous ablation; the second is to consider LA in patients in whom resection or percutaneous ablation are technically infeasible, and TACE and sorafenib are considered in patients in whom the previous options have been judged infeasible according to tumour stage (Table 1).

Because of the shortage of organs in Italy and the strong epidemiological pressure imposed by HCC, LT was considered as the first-line option only in HCC patients of Child–Pugh class C status or in young patients positive for hepatitis B virus infection with multinodular HCC, and was considered as second-line therapy only in patients in whom first-line options had failed for reasons of recurrence or incomplete treatment.

This enrolment policy enabled the provision of LA as a viable alternative to resection and/or percutaneous ablation in patients with BCLC stage A disease, and as a potentially radical therapeutic alternative to TACE in super-selected patients with BCLC stage B disease.

The role of LA in the present treatment algorithm is justified by some of the theoretical advantages afforded by the laparoscopic approach with respect to percutaneous procedures, which include the ability to approach lesions adjacent to the gastrointestinal tract, gallbladder and bile ducts, or in the presence of thrombocytopenia, and the ability to use intraoperative ultrasound to target lesions more accurately.

Liver function in the present study group is indicated by the findings that 50% of patients had MELD scores of $>10$ and 33% had Child–Pugh class B cirrhosis, both of which reflect the present study’s particular enrolment criteria. Thus, the 2-year survival rate of 79% would appear to represent an excellent result.

A recent multicentre Italian study described a 40% recurrence rate in patients with single HCC lesions of $<3.0$ cm treated with RF ablation.
Given that 50% of patients in the present study population had a largest tumour diameter of >2.5 cm and 48% had multinodular HCC, the present 2-year recurrence rate of 55% would also seem to be acceptable.

This consideration is sustained by the present study’s internal comparison with patients submitted to laparoscopic RF ablation. This analysis showed a significant advantage of MW ablation over RF ablation in preventing tumour recurrence at 2 years (Fig. 4) when patients were matched for tumour characteristics.

Some limitations derive from the retrospective nature of this comparison. It should be underlined, however, that the learning curve effect in the LA procedure may be considered negligible in this study because the first 30 LA treatments performed at the study institution were excluded from analysis and all of the surgeons involved had experience with percutaneous RF ablation of ≥10 years. Moreover, the propensity score approach refined all other differences between the study and control groups.

In conclusion, laparoscopic MW ablation proved to be a safe and apparently effective therapy even in patients with moderately impaired liver function who would be considered as suboptimal candidates for resection, percutaneous ablation and TACE. The present findings may be justified by patient super-selection and the favourable physiopathology of minimally invasive approaches; however, larger prospective studies are required to confirm such prognostic results in this therapeutic setting.

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Conflicts of interest

None declared.

References


Supporting information Additional supporting information may be found in the online version of this article at the publisher’s website:

Table S1. Complications after laparoscopic microwave ablation in 42 patients with hepatocellular carcinoma.

Table S2. Radiological efficacy of laparoscopic microwave ablation considered as the complete absence of contrast enhancement in arterial phase computed tomography after contrast medium injection.

Table S3. Features of nodules treated with microwave coagulation therapy. Outcome 1: no contrast enhancement; outcome 2: residual contrast enhancement seen at centralized computed tomography revision.

Table S4. Features of nodules presenting residual contrast enhancement (nodular pattern) in arterial phase computed tomography.