

## Publication History

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## Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of death in the malignant neoplastic diseases in the world. Surgical operation is sometimes not indicated because of complicated liver cirrhosis and extrahepatic disorders. Radiofrequency ablation has been developed as a less invasive treatment for HCC since 1999, and long-term outcome has been shown. There are several complications which should be paid attention, and to improve the prognosis, combination treatment with transarterial chemoembolization should be discussed. Overall survival after between RFA and surgical resection should be compared prospectively. Establishment of staging system for treatment allocation of HCC and prevention of HCC recurrence is important issue to be examined.

## Introduction

Radiofrequency ablation (RFA) has been utilized as a less invasive and curative treatment for the treatment of hepatocellular carcinoma (HCC), and the methods and procedure have been developed. In some countries, it has been chosen as first line treatment for early stage HCC. Long-term prognosis has been reported and the associated factors for the prognosis after RFA have been shown. Several complications were reported after RFA. The prognosis was compared between patients who were treated by between surgical resection and those treated by RFA. The recent developments and future perspective of RFA is discussed in this review.

## Radiofrequency ablation method

Of all therapeutic apparatus compared and evaluated up to now, the RF 3000 generator system (Boston Scientific, Boston, USA) had the most positive therapeutic effects.<sup>1</sup> However, in many articles, an internally cooled single electrode was used.<sup>2</sup> When there was a risk of RFA incurred by

the hepatocellular carcinoma (HCC) location, the therapeutic effects were reduced, in particular the complete response rate was low in the vicinity of the gall bladder and the stomach and intestine, as well as the diaphragm, and in the vicinity of large blood vessels.<sup>3</sup> However, it has been reported that, although the therapeutic effects are not reduced when tumors exist in the vicinity of large blood vessels or adjacent to the extrahepatic organs, attention should be paid to the prevention and control of complications.<sup>4</sup> RFA with the use of artificial ascites for HCC adjacent to the diaphragm and to the stomach and intestine produced sufficient therapeutic effects, thereby improving the sonic window.<sup>5</sup>

When performing RFA, the use of a guiding needle with an external insulated sheath was useful because it allowed for precise tumor targeting.<sup>6</sup> The use of laparoscopic RFA has allowed a sufficient therapeutic effectiveness to achieve complete tumor ablation in all cases when the HCC nodule is located with bulging or at subcapsular area, as well as an adequate safety margin, compared to percutaneous RFA.<sup>7</sup> As shown in [Fig. 1](#), extra-hepatic protruding HCC nodule is the most appropriate indication for laparoscopic RFA, and complete necrosis could be achieved after one treatment session under laparoscopic ultrasound guiding. When RFA was performed under laparoscopy, complete necrosis is usually observed.<sup>8</sup>



**Figure 1.** Hepatocellular carcinoma (HCC) nodule protruding from the liver surface is treated by laparoscopic radiofrequency ablation (RFA) under ultrasound guiding. (a) HCC nodule is directly observed under laparoscopy. (b) Under laparoscopic ultrasound guiding, RFA electrode is introduced to accurate position of the nodule, avoiding damage to diaphragm and intrahepatic vessels. (c) The entire HCC nodule was completely ablated by RFA. (d) Computed tomography (CT) scan before the treatment revealed hypervascular nodule with 2.6 cm in diameter at the surface of the liver. (e) After laparoscopic RFA, complete necrosis was confirmed by CT scan.

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## Assessment of the therapeutic effect of RFA

Although the effect of RFA is, in general, evaluated by dynamic computed tomography (CT) scans taken 1 to 7 days after the procedure, it was possible to assess the therapeutic effect by multidetector row helical CT (MD-CT) immediately after RFA, thereby achieving shorter hospital stays.<sup>9</sup> As well, one report indicates that it was possible to assess the therapeutic effect by contrast-enhanced ultrasonography immediately after RFA.<sup>10</sup> Contrast-enhanced sonography with abdominal virtual

sonography was useful in monitoring the therapeutic effect and reducing the CT scan frequency.<sup>11</sup>

## Prognosis after radiofrequency ablation

According to a report from a single institution in France, RFA was performed in 235 cases, with up to three HCC  $\leq 5$  cm in diameter, and achieved complete ablation in 222 cases. 67 cases were judged potentially resectable according to Barcelona Clinical Liver Cancer (BCLC) criteria; in these patients, RFA treatment produced 76% survival at 5 years. The factors contributing to survival were the prothrombin time and serum alpha-feto protein (AFP) levels. Conversely, the factors related to recurrence were multinodular tumors as well as the AFP level. In this report, RFA could be used as an effective first-line treatment in patients with a single nodule of 5 cm or less, a low serum AFP level, and well preserved liver function.<sup>12</sup>

According to a report from Italy, RFA was performed in 218 cases of single nodule HCC, measuring 2 cm or less in diameter, followed by an analysis of the prognosis. The 5-year survival rate was 68.5%, with a low 1.8% incidence of complications. Compared with resection, it was less invasive and could be conducted at a lower cost. It could therefore be considered the treatment of choice for resectable single HCC  $\leq 2.0$  cm.<sup>13</sup> In Japan, the prognosis of 1000 patients who had undergone RFA was analyzed; the 1, 3, and 5-year survival rates were 94.7%, 77.7% and 54.3%, respectively.<sup>2</sup> According to a report from China, the factors related to the prognosis after RFA were the tumor diameter, the number of tumors, the use of combination therapy with ethanol injection, the margin, and the Child-Pugh score.<sup>14</sup> According to the outcome of RFA treatment for a large single-institution series in Korea, the method had a local recurrence rate of 8.1% at 1 year and 11.8% at 3 years, and patient survival rates were 95.2% at 1 year, 69.5% at 3 years, and 58.0% at 5 years.<sup>15</sup> The five year survival after RFA was similar between Western and Eastern countries (Table 1).

**Table 1. 5-year overall survival after r with operable HCC nodule**

| Overall survival           |                        |
|----------------------------|------------------------|
| Investigator               | Diameter of the nodule |
| N'Kontchou G <sup>16</sup> | ≤ 5 cm                 |
| Livraghi T <sup>17</sup>   | ≤ 2 cm                 |
| Tateichi R <sup>18</sup>   | ≤ 3 cm                 |
| Peng ZW <sup>19</sup>      | ≤ 5 cm<br>≤ 3 cm       |
| Choi D <sup>20</sup>       |                        |

## Prognosis after RFA and the staging system

The Cancer of the Liver Italian Program (CLIP) score and BCLC scoring system more accurately predicted the prognosis than the Okuda score in patients with early-intermediate HCC, undergoing non-surgical therapy, such as RFA.<sup>21</sup> The results of an analysis in Japan demonstrated that, regardless of the CLIP score, the combination of transarterial chemoembolization (TACE)—RFA had the highest 5-year survival.<sup>22</sup> In Japan, where early-stage HCC is prevalent, the majority of cases are classified into CLIP stage 1 of CLIP scores and, as such, the Japanese integrated staging (JIS) score was proposed as a new early HCC staging system.<sup>23</sup> The results of the validation done in many cases demonstrated that the JIS score yielded a better prediction of the prognosis than the CLIP score.<sup>24</sup> It has also been reported from in Korea that the JIS score is the most appropriate score for predicting the prognosis.<sup>25</sup>

## Tumor markers

The tumor marker relevant to the prognosis after RFA is des-gamma-carboxy prothrombin time (DCP) levels; wherein, high DCP levels predicted a poor prognosis after RFA.<sup>16,17</sup> However, the same institution also reported that a comparison of AFP, DCP and AFP-leptin 3 (AFP-L3) demonstrated that AFP-L3 was the most useful indicator of the overall survival and disease-free survival.<sup>18</sup> It was pointed out that the AFP mRNA levels in the blood after RFA are also an objective index of recurrence.<sup>19</sup> On the other hand, blood vascular endothelial growth factor (VEGF) levels

have also been reported to be related to the prognosis.<sup>20</sup>

## Recurrence

Local tumor recurrence after RFA is 9.0% at 1 year and 17.7% at 3 years; therefore, local recurrence is relevant to the prognosis for survival.<sup>26</sup> Evaluation of the therapeutic effects of RFA by contrast enhanced CT scans or by enhanced magnetic resonance imaging (MRI) here demonstrated that the procedure provides good local control and the recurrence rate is low in cases in which the post-ablation margin was 0.4 cm or more and the tumor size was smaller than 2.5 cm.<sup>27</sup> The overall local recurrence rate after RFA was 12.8% and the tumor diameter of >2.5 cm was a significant independent factor.<sup>28</sup> However, another report indicates that even when local recurrence occurred, it did not adversely affect the survival prognosis.<sup>29</sup> Utilizing the RF 3000 generator system has been reported more positive effects than cool-tip electrode.<sup>30</sup>

On the other hand, the cumulative rate of intrahepatic distant recurrence was reported as 10.4% and 77.0% at 1 and 5 years, respectively. In a multivariate analysis, AFP and DCP values, as well as the safety margin, were significant independent factors.<sup>31</sup> The intra-hepatic distant recurrence was associated with multi-nodular lesions and hepatitis C virus (HCV), even after curative ablation was achieved.<sup>32</sup> Recurrence at a distant site is an important, poor prognostic factor.<sup>33</sup> Although it is possible to ensure long-term survival by carrying out repeat RFA after recurrence,<sup>34</sup> the more frequently recurrences occur, the higher the risk for subsequent recurrence becomes.<sup>35</sup> Histological grade is relevant to the therapeutic efficiency of RFA and also plays a part in determining survival.<sup>36</sup>

## Prognosis and possible measures to improve survival after RFA

Long-term interferon maintenance therapy improved the survival in patients with HCV related HCC after RFA.<sup>37</sup> On the other hand, the administration of lamivudine after RFA for hepatitis B virus (HBV)-related HCC maintained the liver function and was also safe.<sup>38,39</sup> The administration of vitamin K for HCV-related HCC did not produce a chemopreventative effect.<sup>40</sup> The oral administration of a branched-chain amino acid after RFA made it possible to maintain the serum albumin levels and it was also useful for improving the liver function.<sup>41</sup>

## Resection versus RFA

With regard to the question of whether surgical resection or RFA is superior, two randomized comparisons have been reported—all from China. In these reports, the life prognoses of single HCCs of 2 cm or less diameter were randomly compared between RFA and resection. It was reported that

there would be no difference between the two, or that, for single HCC of 5 cm or less, there was no difference in terms of both disease-free survival and overall survival.<sup>42,43</sup> In Italy, a group of 109 patients who underwent RFA and a group of 91 patients who underwent resection were compared retrospectively; there was no difference in terms of the overall survival and disease-free survival, for HCC of 3 cm or less.<sup>44</sup> Likewise, a retrospective analysis conducted in Korea, compared a group of 55 patients who underwent RFA treatment for single HCC 4 cm or less and well-preserved liver function with a group of 93 patients who underwent resection; the authors concluded that there was no difference in terms of overall survival and recurrence-free survival at 1 year and 3 years after RFA.<sup>45</sup> When laparoscopic RFA was performed on patients with single HCC nodule with Child-Pugh A liver function, RFA and resection had similar survival rates.<sup>46,47</sup>

However, a case control study of resection versus RFA showed that recurrence, tumor diameter, and whether resection or RFA were performed, all affected overall survival. The authors concluded that a resection provided some advantages.<sup>48</sup> Furthermore, with regard to cases of HCC which are not suitable candidates for liver transplantation, a Markov model was used to compare the life-adjusted survival between resection and RFA. The survival rate in the resection group was 5.33 years, while in the RFA group it was 3.91 years. It was concluded therefore, that patients treated by a resection would have a better survival rates.<sup>49</sup> In another study, 79 cases of resection and 79 cases of RFA treated at two different institutions were compared. The result showed that resection would be better than RFA for tumors of 3 cm and larger in diameter with Child A score, but that the overall survival would be the same for surgery and RFA in the case of Child B score.<sup>50</sup>

## Comparison between RFA and other ablations

A comparison between microwave coagulation and RFA for HCC, 2 cm or less in tumor diameter demonstrated that RFA was superior because it created a larger necrotic area, resulting in a lower local recurrence rate; this conferred better cumulative survival, while bile duct injury and pleural effusion occurred less frequently.<sup>51</sup>

Another study compared percutaneous ethanol injection (PEI) and RFA. This randomized controlled trial (RCT) conducted in Taiwan demonstrated that RFA required fewer treatment sessions to achieve complete tumor necrosis, and provided better overall survival.<sup>52</sup> Another RCT between PEI and RFA was conducted in Japan. The 4-year survival rates were 74% for RFA versus 57% for PEI, resulting in RFA treatment being associated with a lower risk of death and recurrence. There was no difference in frequency of adverse events.<sup>53</sup> Although it was not RCT, another study compared PEI and RFA and found that local recurrence rates after RFA were lower.<sup>54</sup> An RCT conducted in Italy compared RFA with PEI and found that complete response of RFA after one year was associated with a better outcome, though no survival advantage was observed.<sup>55</sup>

There have been three meta-analyses, based on RCT comparing the effects and complications

between RFA and PEI. Each found that RFA had better overall survival, while PEI had a higher local recurrence rate; thus RFA was superior in cancer-free survival rates.<sup>56-58</sup> No difference was observed in the complications between the two.

RCT was conducted to identify whether a combination of RFA and PEI would produce a better outcome than RFA alone. For tumors measuring between 3.1 cm and 5 cm in size, RFA + PEI improved patient survival, and overall recurrence was lower with combination treatment.<sup>59</sup>

## Combined TACE and RFA treatment

The combination of transarterial embolization (TAE) and RFA or PEI was compared with TACE alone, and it was found that TACE + RFA had a better prognosis.<sup>60</sup> The results of a case-control comparison between RFA combined with TACE and RFA alone demonstrated that there was no difference in cases of single HCC  $\leq 5$  cm, but that the TACE + RFA combined treatment had a higher survival rate in cases of single HCC  $> 5$  cm or multiple tumors.<sup>61</sup> The combination of TACE and RFA was technically successful in 88% of cases; such patients, complete the therapy after a single treatment session.<sup>62</sup> In addition, the combination of TACE and RFA produced high local control rates.<sup>63</sup> TACE and RFA has been performed for HCC immediately below the diaphragm, and found to be effective.<sup>64</sup> The combination of bland arterial embolization with RFA and a resection has also been compared; the overall survival was found to be similar in patients with single HCC measuring up to 7 cm in diameter.<sup>65</sup>

The extent of necrosis resulting from RFA increases when combined with hepatic arterial balloon occlusion.<sup>66</sup> Furthermore, combined treatment with balloon occlusion after transcatheter arterial infusion chemotherapy (TAI) is effective in expanding the necrotic area.<sup>67</sup> However, some researchers argue that this combination is not necessary because the effects of the combined therapy involving TACE and RFA, and that of RFA alone, for small HCC  $\leq 3$  cm, are the same.<sup>68</sup>

## Complications

Data from 3891 cases were collected in a joint study conducted in Osaka, Japan. Complications were observed in 207 cases (7.9%), with 9 patients dying within 3 months. The causes of death in these cases were: liver failure in 3 cases, rapid progression in 3 cases, biliary injury in 1 case, gastrointestinal bleeding in 1 case, and myocardial infarction in 1 case.<sup>69</sup> Data for 255 cases in China have also been reported, with major complications observed in 31 cases (10%) as follows: 13 cases of liver failure, 10 cases of hydrothorax, 2 cases of tumor seeding, 1 case of upper gastrointestinal bleeding, and one each of intrahepatic abscess, bile duct injury, and cardiac arrest, 5 cases of hyperglycemia, and 11 cases of death due to liver failure.<sup>70</sup> A report from the United States noted that complications had been observed in 7 out of 91 cases as follows: 2 cases of hepatic abscess and one each of skin burn, hemorrhage, myocardial infarction, and liver failure.<sup>71</sup> According to the

results of a multicenter survey conducted in Korea, liver abscess (0.66%), peritoneal hemorrhage (0.46%), biloma (0.20%), ground pad burn (0.20%) and pneumothorax (0.20%) were reported as complications.<sup>72</sup>

## Liver abscess and bile duct injury

Liver abscess is the most common complication—de Raere *et al.* observed 7 cases out of 350 sessions and a high risk of this complication among patients with a previous bilioenteroc anastomosis.<sup>73</sup> Likewise, Choi *et al.*<sup>74</sup> and Elias *et al.*<sup>75</sup> also reported that liver abscess was seen more often in cases of biliary abnormality, as well as after TACE treatment. In one report, cholangitis and liver abscess occurred simultaneously.<sup>76</sup> Attention should therefore be paid to the fact that the risk for liver abscess complication is high in cases of complicated anastomosis of the bile duct to the intestinal tract.

Biliary stricture was observed in 7 cases after the RFA procedure, with liver abscess as a complication in 3 cases.<sup>77</sup> It was reported that intraductal chilled saline perfusion by endoscope had been effective in preventing bile duct injury.<sup>78</sup>

## Bleeding

A total of 4133 RFA treatments were performed in 2154 cases, with hemorrhagic complications occurring in 63 treatments (1.5%) as follows: hemoperitoneum (0.7%), hemothorax (0.3%) and hemobilia (0.5%). In addition, there were two deaths due to hemoperitoneum.<sup>79</sup> Poggi *et al.* reported only one case of bleeding that required surgery.<sup>80</sup> Attention has also been focused on bleeding which occurred in one case of subcapsular liver tumor, but there were no complications such as seeding.<sup>81,82</sup>

## Intestinal injury

Two cases were reported in which colonic perforation occurred as a complication on the 8<sup>th</sup> day after RFA. Attention should be paid to the fact that intestinal injury was indolently present.<sup>83,84</sup> Another report indicated the occurrence of duodenopleural fistula formation as a complication.<sup>85</sup>

## Hepatic infarction

Hepatic infarction has been observed after RFA; the frequency is 1.8%.<sup>86</sup> The use of internally cooled electrodes is a risk. In addition, portal thrombosis has also been reported to occur.<sup>73,87</sup>

## Seeding



A report given by Llovet *et al.* in 2001 on the high rate of seeding after RFA has received much attention. The risk factors included: subcapsular tumor localization, a high degree of poor differentiation, and a high baseline AFP.<sup>88</sup> Since then the risk of seeding after RFA, has been attributed to subcapsular location, poorly differentiated tumors and high AFP levels.<sup>89,90</sup> However, a discrepancy exists between institutions, with some arguing that, in reality, seeding is exceptionally rare.<sup>91,92</sup> In order to prevent seeding, tract ablation should therefore be properly performed.

## Other complications

In another report, pneumothorax occurred after RFA, and so careful attention is required for tumors adjacent to the diaphragm.<sup>93</sup> It has been reported that myoglobinuria occurs as a complication after RFA and that the serum creatinin level rises, making it necessary for attention to be paid thereto.<sup>94</sup> Another case was reported in which hemolysis occurred, thus inducing hemogeobinuria as a complication.<sup>95</sup> There have also been reports that rapid tumor progression occurred after RFA;<sup>96,97</sup> however, the actual frequency was low and it is therefore necessary to investigate whether or not it was indeed a complication associated with RFA.

We have done 1440 sessions of RFA to patients with early stage HCC from July, 1999 to December 2009. The complications have been analyzed as shown in [Table 2](#). The complication rates were 1.8% and 1.9% when the patients were treated by laparoscopic or percutaneous RFA, respectively.

**Table 2. Complications by laparoscopy at Red-Cross hospital (from July, 1999 to 1**

|                              | Laparoscopy<br>(n = 107) |
|------------------------------|--------------------------|
| Bile duct damage             | 0 (0%)                   |
| Liver abscess                | 1 (0.9%)                 |
| Inter-costal arterial injury | 0 (0%)                   |
| Hemothorax                   | 0 (0%)                   |
| Hepatic infarction           | 0 (0%)                   |
| Hepatic dysfunction          | 0 (0%)                   |
| Skin burn                    | 0 (0%)                   |
| Subcutaneous hematoma        | 1 (0.9%)                 |
| Pneumothorax                 | 0 (0%)                   |
| Gastrointestinal perforation | 0 (0%)                   |
| Total                        | 2 (1.8%)                 |

## Conclusion

RFA is promising for improving patient survival with early stage of HCC when performed skillfully to avoid serious complication. To prevent the recurrence of HCC is the most important issue for achieving better survival.

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