Radiofrequency Ablation for Liver Tumors

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Introduction

Currently, radiofrequency ablation (RFA) has been widely accepted therapy in the management of primary and metastatic liver tumors. RFA can provide excellent local therapeutic effects especially in the small liver tumors. However, RFA for the large liver tumors is still challenging and various efforts have been made to enhance the therapeutic response. Moreover, although RFA is considered as a relatively safe procedure, it has a potential to induce severe complications. Therefore, it is important to make utmost efforts to avoid complications.

In this lecture, some technical tips to enhance the therapeutic response as well as to prevent the complication of liver RFA will be reviewed. Additionally, current clinical outcomes of liver RFA will be introduced.

Enhance the local therapeutic response

To achieve good local therapeutic response is important because it is significantly linked with patient’s survival. Tumor size is the most important factor affecting local therapeutic response. Livraghi et al. reported that complete disappearance of tumor enhancement was obtained in 90% of small hepatocellular carcinomas (HCCs) (≤3cm), 60% of medium HCCs (3.1-5cm), and 24% of large HCCs (>5cm). Similarly, Nielsen et al. reported that frequency of incomplete ablation was 9% (≤3cm), 27% (3.1-5cm), and 45% (>5cm) of metastatic liver tumor from colorectal cancer (CRC). Tumor location is another important factor affecting local therapeutic response. Liver tumors are sometimes located in so-called “difficult locations” those are close to diaphragm, large vessels, and GI tracts. Ablative margin for those tumors are sometimes insufficient, resulting in the incomplete ablation or local recurrence. Yang W, et al. reported that local recurrence was significantly higher if liver tumors are located in the difficult locations.

To enhance the local therapeutic response of liver RFA, several attempts have been made. Combination of hepatic artery embolization is one of the most effective approaches to enhance therapeutic response. Theoretically, hepatic artery embolization blocks the arterial blood flow of liver tumor and surrounding liver tissue, resulting in the enhancement of ablative zone. Takaki et al. reported that complete ablation could be achieved in all HCCs measuring 5.1-10 cm when chemoemboization was combined. This approach is also useful in the management of metastatic liver tumor. Recently, Yamakado et al. reported the utility of RFA combined with hepatic arterial chemoembolization using degradable starch microsphere mixed with mitomycin C.
Results of their study showed that the 2-year local tumor control rate was 92.0% and median survival time was 48.4 months \(^1\). Combination use of percutaneous ethanol injection (PEI) is another approach to enhance the local therapeutic response. Kurokouchi et al. reported that ablative zone volume was significantly expanded when PEI was combined with RFA as compared with RFA alone. Other approaches to enhance the therapeutic response of RFA include the use of switching controller and the combination use of molecular targeting drugs such as sorafenib.

**Prevention of complications**

Livraghi et al. reported the complications of liver RFA in 2,320 patients with 3,554 liver tumors\(^1\). The mortality rate of liver RFA was 0.3% with their causes of gastrointestinal (GI) tract perforation, peritonitis, tumor rupture, and liver failure. The major complication rate was 2.2%. The most frequent major complications were hemorrhage (0.5%) and tumor seeding (0.5%) followed by liver abscess (0.3%), and bowel perforation (0.2%). Takaki et al. reported the complications of 1,500 CT-fluoroscopy guided liver RFA sessions\(^3\). In their study, the mortality rate was 0.1% because of liver failure subsequent to hemorrhage. The major complication rate was 2.8% and the hemorrhage was the most frequent complication (1.1%). According to these studies, hemorrhage and GI tract perforation are the most frequent severe complications.

To prevent the hemorrhagic complication, patient with abnormal coagulability should be excluded from the indication of liver RFA. In general, platelet counts <40-50\(\times\)10\(^9\)/L and/or an international normalized ratio exceeding 1.5 are benchmarks of abnormal coagulability. Combination use of chemoembolization is useful in avoiding hemorrhagic complications. Takaki et al. reported that the absence of arterial embolization before RFA was identified as one of the significant risk factors for major hemorrhage\(^3\).

To prevent the GI tract perforation, it is important to move away the GI tracts from the target lesion to avoid the collateral damage from RFA. Changing the patient’s body position should be tried in the first place, if GI tracts are located adjacent to the target tumor. Injecting water or carbon dioxide gas as well as balloon catheter interposition is another option to prevent the GI tract injury\(^4\). Recently, Hasegawa et al. reported that hyaluronic acid gel injection is useful in separating the target lesion and GI tract\(^5\).

**Therapeutic outcomes**

Currently, many studies have confirmed that RFA is a useful therapeutic option in the management of HCCs. Recent studies have shown that overall and disease free survival rates after RFA for early to intermediate stage HCCs were 50-60% and 18-39% at 5-years, and 24-34% and 4-25% at 10-years, respectively (Table 1) (10, 16-20). These promising results opened the debate on whether RFA can be offered as
the alternative treatment to hepatectomy. Some retrospective studies and randomized controlled trials have been performed to compare the RFA and hepatectomy\(^8,21\). Yamakado et al. retrospectively compared the outcomes of RFA combined with chemoembolization and hepatectomy for HCCs within the Milan criteria\(^8\). Results of their study showed that RFA combined with chemoembolization provide similar oncologic outcomes to hepatectomy. Recent meta-analysis conducted by Wang et al. concluded that the effectiveness of RFA is comparable to hepatectomy especially in very early stage HCCs\(^21\). However, available randomized and non-randomized studies include some sort of biases, and high-quality randomized controlled trials (RCT) are still lacking. In Japan, nationwide RCT comparing survival between RFA and hepatectomy for patients with resectable HCCs of 3 cm or less in size and up to three nodules is underway\(^22\).

RFA has also been played important roles in the management of CRC liver metastases. Recent studies have shown that 5-year overall survival rates after RFA for CRC liver metastases were 3-34% with median survival time of 14-35 months (Table 2)\(^23-27\). Although there have been no randomized controlled trials, there are some retrospective studies those compared the outcomes of RFA and hepatectomy. Most of those studies suggested that hepatectomy provides better local and survival outcomes as compared to RFA\(^28\). Therefore, the role of RFA may be limited in the treatment of resectable liver metastasis, although the well-designed randomized controlled trial will be necessary to confirm those results. RFA is also performed as the palliative treatment of non-resectable CRC liver metastasis. RCT which compared the RFA plus systemic treatment versus systemic treatment alone for non-resectable colorectal liver metastasis showed that RFA plus systemic treatment resulted in significant longer progression-free survival than systemic treatment alone\(^29\). Although no significant difference in overall survival were not found in their initial analysis\(^29\), their long term results presented later showed the significant differences in the 8-year overall survival rates (35.9% for RFA and systemic therapy vs 8.9% for systemic therapy alone, \(p=0.010\))\(^30\).

Conclusions

RFA is a powerful tool in the management of both primary and metastatic liver tumors. Technical tips and knowledge introduced in this lecture will be helpful to maximally utilize this promising therapeutic option.

References

2. Radiofrequency Ablation for Liver Tumors (Haruyuki Takaki, MD, PhD)


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<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patient No.</th>
<th>Tumor characteristics</th>
<th>Treatment</th>
<th>Local recurrence</th>
<th>Overall survival 5-year</th>
<th>10-year</th>
<th>Recurrence-free survival 5-year</th>
<th>10-year</th>
<th>MST (months)</th>
</tr>
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<tbody>
<tr>
<td>Yang W</td>
<td>2016</td>
<td>316</td>
<td>≤3 tumors, ≤5 cm</td>
<td>RFA</td>
<td>13.8%</td>
<td>49.7%</td>
<td>28.4%</td>
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<tr>
<td>Kim GA</td>
<td>2015</td>
<td>331</td>
<td>Single, ≤3 cm</td>
<td>RFA</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>39.4%</td>
<td>25.1%</td>
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<tr>
<td>Zhang L</td>
<td>2015</td>
<td>837</td>
<td>≤3 tumors, ≤3 cm</td>
<td>RFA</td>
<td>...</td>
<td>55.2%</td>
<td>34.2%</td>
<td>30.1%</td>
<td>15.2%</td>
<td>68</td>
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<tr>
<td>Kim YS</td>
<td>2013</td>
<td>1305</td>
<td>≤3 tumors, ≤3 cm; or</td>
<td>RFA</td>
<td>19.4%</td>
<td>59.7%</td>
<td>32.3%</td>
<td>17.5%</td>
<td>3.8%</td>
<td>75</td>
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<tr>
<td>Fujimori M</td>
<td>2013</td>
<td>277</td>
<td>≤5 tumors, ≤5 cm</td>
<td>TACE+RFA</td>
<td>5.4%</td>
<td>56.3%</td>
<td>23.5%</td>
<td>22.5%</td>
<td>9.3%</td>
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<tr>
<td>Shiina S</td>
<td>2012</td>
<td>1170</td>
<td>Mean, 1.8±12 tumors</td>
<td>RFA/TACE+RFA</td>
<td>2.9%</td>
<td>60.2%</td>
<td>27.3%</td>
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</tbody>
</table>

RFA, radiofrequency ablation; HCCs, hepatocellular carcinomas; MST, median survival time; TACE, transcatheter arterial chemoembolization
# Table 2. Results of RFA for CRC liver metastases

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patient No.</th>
<th>Tumor characteristics</th>
<th>Treatment</th>
<th>Local recurrence</th>
<th>Overall survival (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamakado K</td>
<td>2017</td>
<td>25</td>
<td>≤3 tumors, ≤3 cm; or Single, ≤5 cm</td>
<td>TACE+RFA</td>
<td>12%</td>
<td>81.7% 33.7%</td>
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<tr>
<td>Hamada A</td>
<td>2012</td>
<td>84</td>
<td>Single, 55% ≤3 cm, 63%</td>
<td>RFA</td>
<td>41.7%</td>
<td>44.9% 20.8%</td>
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<td>Gillams AR</td>
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<td>192</td>
<td>≤5 tumors, ≤5 cm</td>
<td>RFA</td>
<td>…</td>
<td>40% 18%</td>
<td>28</td>
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<tr>
<td>Gillams AR</td>
<td>2009</td>
<td>117</td>
<td>&gt;5 tumors and/or &gt; 5 cm</td>
<td>RFA</td>
<td>…</td>
<td>13% 3%</td>
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<tr>
<td>Hur H</td>
<td>2009</td>
<td>25</td>
<td>Single Mean, 2.5 cm</td>
<td>RFA</td>
<td>28.0%</td>
<td>60.0% 25.5%</td>
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<tr>
<td>Veltri A</td>
<td>2008</td>
<td>122</td>
<td>≤5 tumors, ≤5 cm</td>
<td>RFA</td>
<td>26.3%</td>
<td>38% 22%</td>
<td>31.5</td>
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</tbody>
</table>

RFA, radiofrequency ablation; CRC, colorectal cancer; MST, median survival time; TACE, transcatheter arterial chemoembolization