Cost-effectiveness of radiofrequency ablation and surgical therapy for small hepatocellular carcinoma of 3 cm or less in diameter

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of radiofrequency ablation (RFA) versus hepatic resection for the treatment of hepatocellular carcinoma (HCC) of 3 cm or less in diameter. RFA was performed using a radiofrequency interstitial tumour ablation system, the cooltip system, or a radiofrequency tumour coagulation system. Hepatic resection was performed under intraoperative ultrasonographic monitoring and guiding.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with a small HCC of 3 cm or less in diameter. Patients were required to have HCC with a definitive diagnosis by either typical hypervascular radiological features or histology through needle biopsy.

Setting
The setting was a hospital. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness and resource use data were gathered from March 1999 to April 2003. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that included in the effectiveness analysis.

Study sample
Power calculations, if performed, were not reported. A total of 290 eligible patients were identified at the authors' institution from March 1999 to April 2003. Of these, 153 underwent percutaneous RFA therapy as curative treatment, 60 underwent surgical resection, 45 had transcatheter arterial embolisation, and the remaining 32 were treated with ethanol injection, microwave coagulation therapy, or other palliative types of treatment. Thus, a total of 213
consecutive patients with a small HCC, who underwent either RFA or surgery, were considered in the current study. It appears that no patient refused to participate or was excluded from the study sample for any reason. There were 144 men and 69 women, and the median age of the whole sample was 65 years (range: 38 - 87). There were 101 men and 52 women in the RFA group, 43 men and 17 women in the surgery group. The median ages were 66 years (RFA group) and 64 years (surgery group), respectively.

**Study design**
This was a prospective cohort study that was carried out at a single centre, the Department of Gastroenterology of the Toranomon Hospital in Tokyo. The choice of treatment depended mainly on liver function and the site of the tumour in the liver. A tumour situated deep in the liver was usually treated with RFA, while a superficial tumour was more often treated with surgical resection. The average length of follow-up was 2.6 years. Only 2 patients were lost to the follow-up assessment. Blinding was not performed. The patients were observed every 4 weeks after the first treatment. Liver function test, haematology, and tumour markers were measured every month. Recurrence was surveyed by computed tomography (CT) imaging every 3 months.

**Analysis of effectiveness**
The analysis of the clinical study appears to have been based on all patients who were included in the initial study sample. The primary outcome measures were:

- judgement of necrotic area after RFA and judgement of resected area and pathology after surgery;
- incidence and manners of recurrence;
- side effects; and
- mortality.

Judgement of necrotic area was classified into three categories. Grade 1 corresponded to a necrotic area smaller than the original tumour size. Grade 2 corresponded to a necrotic area of the same size or larger than the original tumour, but no safety margin of 5 mm around tumour. Grade 3 corresponded to a necrotic area larger than the original tumour size, with a safety margin of 5 mm or more in all directions.

The study groups were comparable at baseline in terms of their demographic and clinical characteristics. However, the rate of decompensated cirrhosis was slightly higher in the RFA group, the indocyanine retention rate at 15 minutes was significantly higher in the RFA group, while platelet count was significantly higher in patients receiving surgery. Details of HCC were also quite comparable between groups, although patients with a recurrent tumour tended to receive RFA therapy more frequently. Although tumour size was slightly larger in the surgery group, multiple tumours were more frequent in the RFA group.

**Effectiveness results**
Judgement of necrotic area after first RFA therapy was 2 (1.3%) Grade 1, 89 (58.2%) Grade 2, and 62 (40.5%) Grade 3.

Among 91 patients with Grades 1 and 2, additional ablation therapy was performed in 52 patients (57.1%). Thirty-seven patients received therapy twice, 11 patients three times, and 4 patients four times or more as an initial session of locoregional therapy.

Of the 52 patients with additional therapy, 31 patients (59.6%) accomplished Grade 3 necrosis and the other 21 (40.4%) showed Grade 2 necrosis.

At the end of the initial session of RFA, 60 (39.2%) attained Grade 2 necrosis, 93 (60.8%) achieved Grade 3, and none remained at Grade 1.
All the tumours in 60 patients with hepatic resection were completely removed on dynamic CT films after surgery.

The cumulative recurrence rate in patients with RFA was 16.6% at the end of the first year, 40.3% at the second year, and 50.2% at the third year. The corresponding rates in patients with surgical resection were 14.9% (end of first year), 27.1% (second year) and 30.3% (third year), respectively.

The recurrence rate in patients with RFA therapy was higher than that of surgical resection, (p=0.069).

The recurrence rate was higher in patients with a "recurrent" tumour than in those with an "initial" tumour.

When local recurrence rates were calculated in patients with RFA therapy, the 1-year recurrence rate was 4.4%, the second year rate was 7.9%, and the third year rate was 7.9%. The corresponding rates in patients with surgery were 0% (first year), 0% (second year) and 0% (third year).

The local recurrence rate in patients after RFA therapy was higher than that of surgical therapy, (p=0.053).

The relationship between necrotic area and recurrence after RFA therapy was analysed in detail. For example, the recurrence rate was significantly higher in patients with Grade 2 than in those with Grade 3.

Rates of recurrence-free patients, recurrence at different sites, and local recurrences were calculated on the basis of the need for repeated ablation. The rates were as follows.

With surgery: recurrence-free, 72%; recurrence at different sites, 28%; and local recurrence, 0%.

With RFA: recurrence-free, 62%; recurrence at different sites, 30%; and local recurrence, 8%.

The most common side effects with RFA were abdominal pain, fever, and mild aggravation of liver function tests. Surgery led to biloma with infection, ascites, bleeding, and aggravation of liver functions.

No treatment-related death was observed, although 10 patients (4.7%) died during the follow-up period. Six of these were in the RFA group and 4 in the surgery group.

Clinical conclusions
The effectiveness analysis showed that RFA led to recurrence rates higher than those of surgery. However, malignant features at the time of recurrences were not observed. Further, additional ablation significantly reduced local recurrences.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was carried out.

Direct costs
The perspective adopted in the study was unclear. The authors stated that a societal perspective was used, but only the direct medical costs were included in the study. The analysis considered the costs associated with diagnosis and pre-treatment check-up (e.g. biochemistry, haematology, virology, procedures for treatment (e.g. anaesthesia, medicines, materials), post-treatment care and examination (e.g. antibiotics, medications, wound care), and hospital stay. The unit costs and the quantities of resources used were not presented separately. The source of the costs was not explicitly reported but it might have been the authors' institution. The resource use data came from the sample of patients included in the effectiveness study. Discounting was not applied, despite the fact that it might have been relevant as some costs were incurred during longer than two years. The price year was not reported.

Statistical analysis of costs
Standard statistical analyses were carried out to test the statistical significance of cost-differences.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
Japanese yen (JPY). The exchange rate from US dollars ($) to Japanese yen in October 2005 was $1 = JPY 114.

**Sensitivity analysis**
Sensitivity analyses were not presented in the article, although the authors stated that some sensitivity analyses were, in fact, carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The median admission period was 26 days (range: 11 - 112) for RFA therapy versus 52 days (range: 28 - 187) for surgery. The median hospital stay was 12 days (range: 11 - 112) after RFA therapy versus 26 days (range: 16 - 138) for surgery.

The total costs per patient were JPY 1,745,100 with surgery and JPY 930,100 with RFA.

The cost of RFA was JPY 849,900 for patients who had a single intervention and JPY 1,086,000 for patients who had a repeated intervention.

**Synthesis of costs and benefits**
A synthesis of the costs and benefits was not relevant given that a cost-consequences analysis was carried out.

**Authors' conclusions**
Radiofrequency ablation (RFA) was cost-effective in comparison with hepatic resection in the treatment of small hepatocellular carcinoma (HCC) in Japan.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear. A detailed description of the two interventions was provided. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The clinical data were estimated from a cohort study. However, a randomised trial would have been a more appropriate design in terms of reducing potential selection bias and confounding factors. The study groups were not perfectly matched at baseline, as some laboratory values were significantly different between groups. The evidence came from a single institution, which might limit the representativeness of the study sample. Only 2 patients were lost to follow-up; the length of follow-up appears to have been appropriate. No justification for the size of the sample was provided and power calculations were not reported. These issues tend to limit the internal validity of the study.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
There was limited information on the cost analysis. Although the authors stated that they had adopted a societal cost/resource boundary, only the direct medical costs were included. Details of the methods used to calculate the costs, such as unit costs, source of data and price year, were not reported. Statistical tests were used to test the significance of cost-differences, but no sensitivity analysis of the costs was carried out. In general, the analysis of the costs was carried out unsatisfactorily.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other setting. Sensitivity analyses were not carried out, which further limits the external validity of the study. The analysis referred to patients with small HCC and this was reflected in the authors’ conclusions. The authors stated that a cost-utility analysis was performed, but no data on patient quality of life were provided and no incremental ratios were calculated. Thus, in reality, a cost-consequences analysis was carried out.

Implications of the study
The study results supported the use of RFA for the treatment of small HCC. However, caution is required when interpreting the results of the study given the limitations of the analysis (as highlighted in the commentary). The authors noted that complementary surgery should be applied depending on the location of the tumour, liver function, and background features of the host. The authors suggested that future studies should evaluate the quality of life for patients with small HCC.

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