Is radiofrequency ablation treatment a clinically and cost effective treatment to be offered to people with renal cancer in NHSScotland?

What is an evidence note

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in an approximately 3 month period. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review but do not undergo external consultation. Evidence notes do not make recommendations for NHSScotland.

Health technology description

Typically, people with the early stages of renal cancer have few symptoms, although these develop as the disease progresses. With the advancement of modern imaging techniques, the incidental diagnosis of smaller tumours is increasing. Conventional treatment for renal cancer (also referred to as renal cell carcinoma (RCC)) is total or partial nephrectomy (open or laparoscopic). However, non-resectional ablative procedures such as radiofrequency ablation (RFA) may be selected for small tumours (<4 cm in diameter).

RFA is available for patients with localised RCC or small renal masses that are ideally <4 cm in diameter. It may also be considered in patients who are not suited to surgery (e.g., due to age or significant co-morbidity), or patients in whom there is a need for nephron-sparing treatment (e.g., those with a single kidney, or a genetic predisposition to multiple tumours). There is an increasing awareness of the importance of preserving renal function, with reductions in glomerular filtration rate being associated with increased risk of death. Relative contraindications to RFA include a life expectancy of <1 year, the presence of distant metastases, tumours >5 cm, or tumours in the hilum or central collecting system.

Epidemiology

In the United Kingdom (UK) in 2007, 8,228 people (including 797 from Scotland) were diagnosed with renal cancer. In Scotland, it is the tenth most common cancer in males, and the ninth in females. Incidence has increased across the world.
16% for males and of 26% for females) in incidence in the last 10 years. This may be partly explained by improvements in imaging technologies, leading to an increase in incidental diagnosis of some tumours.

In England and Wales almost 90% of malignant kidney tumours arise in the renal parenchyma. The remaining 10% occur in the renal pelvis or the ureter, and cannot be treated with RFA. The risk of renal cancer increases with age, and obesity and cigarette smoking are established risk factors. Furthermore, the disease is more common in men (ratio 3:2), and in people with certain genetic or medical conditions (e.g., acquired cystic kidney disease). Often patients with localised RCC have competing co-morbidities, which can influence mortality.

In 2008, 3,848 people died from renal cancer in the UK (including 418 from Scotland), accounting for approximately 2% of all cancer deaths. Observed survival rates for Scottish patients diagnosed between 2003 and 2007 were 66.1% at 1 year, 49.4% at 3 years, and 43.5% at 5 years. Survival rates decrease with advancing age.

Safety

Safety outcomes for RFA are poorly reported. The National Institute for Health and Clinical Excellence (NICE) interventional procedure guidance reports on some safety issues highlighted in case series. These include haemorrhage in 6% of patients (Gervais et al., 2005); haematoma rates of between 1% and 12% (Hegarty et al., 2006; Zagoria et al., 2007); ureteric strictures after 1–2% of procedures (Breen et al., 2007; Gervais et al., 2005; Zagoria et al., 2007); urionoma in <1% of cases (Breen et al., 2007; Gervais et al., 2005); and one case (out of 87) of thermal injury to the duodenum that required laparotomy (Breen et al., 2007).

The NICE guidance also referred to case reports of life-threatening delayed haematuria requiring transcatheter embolisation (Roach et al., 2006); ureteropelvic junction obstruction resulting in nephrectomy (de Arruda et al., 2006); and nuemuscular injury, pneumothorax, infarction and inflammatory tract mass.

Clinical effectiveness

The most recent evidence on RFA for renal tumours comes from NICE interventional procedure guidance published in 2010. This guidance recommends that: ‘current evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) for renal cancer in the short and medium term appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit, and that patients are followed up in the long term’. This is based on a meta-analysis, three non-randomised comparative studies, five case series and five case reports.

The meta-analysis reported on by NICE, by Kunkle et al., evaluated cryoablation (an ablative procedure which involves freezing the targeted tissue) and RFA as primary treatment for small renal masses (≤4 cm). It included 47 studies (case series evidence), including 1,375 tumours treated by RFA (n=775) and cryoablation (n=600). The authors reported that the rates of local tumour progression (defined as radiographic or pathologic evidence of residual disease after initial treatment, regardless of the time to recurrence) were higher for RFA compared with cryoablation at a mean 19 month follow up (12.9% versus 5.2%; p<0.0001); repeat ablation was performed more often after RFA (8.5% versus 1.3%; p<0.0001); and metastases were reported more often after RFA, though the difference was not statistically significant (2.5% versus 1.0%; p=0.06). The authors conclude that both approaches are viable based on short-term oncological outcomes, and that the current data suggest that cryoablation results in fewer retreatments and improved local tumour control. However, there are several issues with this review that prevent firm conclusions from being drawn, for example: it is based on case series evidence which is prone to bias; the included studies reported that cryoablation was normally performed laparoscopically (65%) and RFA percutaneously (94%), which may influence differences in success; and the studies included a short post-treatment follow up (mean 18.7 months).

Of the three non-randomised comparative studies referenced by NICE, the first (n=233) reported that 11% of tumours in patients receiving percutaneous RFA had residual or recurrent tumour on follow-up MRI scans (1 year median follow up), compared with 2% of
tumours in those who received laparoscopic cryotherapy (3 year median follow up) (Hegarty et al., 2006). The second (n=264) reported radiographic success of 85% for percutaneous RFA and 90% for laparoscopic cryoablation at 6 months (Weight et al., 2008). The third (n=37) concluded that health-related quality of life was not reduced in patients 1 week after percutaneous RFA, but some quality of life scores (functional functioning, role-physical functioning and role-emotional functioning) reduced in those who received laparoscopic radical nephrectomy (Onishi et al., 2007). The case series and case reports summarised by NICE do not add considerably to the evidence already presented, and the full guidance should be referred to for more details.

An overview published in Australia in 2010 reports on largely the same body of evidence as NICE. It includes the meta-analysis by Kunkle et al., and a review by Long and Park (2009). The methodology used by Long and Park is not clearly described, and so it cannot be regarded as a systematic summary of the available evidence. It included 24 studies, and assessed the reablation rates for RFA and cryoablation stratified in terms of surgical approach (ie open, laparoscopic and percutaneous). The authors reported that for RFA, the percutaneous approach was used most commonly (80%) and for cryoablation, the procedure was normally done laparoscopically (76%). The mean tumour size, cancer-specific survival rates, mean follow-up duration, and salvage nephrectomy rates were not statistically different between RFA and cryoablation. More reablations were required for RFA than for cryoablation (7.4% versus 0.9%; p=0.009). However, the authors state that superiority of RFA or cryoablation remains undetermined, and that prospective randomised studies are required before more definitive conclusions can be drawn.

A number of other reviews are available, including another meta-analysis by Kunkle et al. These do not add considerably to the evidence already presented, and are all limited by the fact that they are based mainly on case series evidence.

There is a need for more robust evidence, with longer follow-up periods, on the use of RFA for renal cancer. Five trial protocols were identified by the authors of one of the reviews and more definitive conclusions may be possible when the results of these are published.

Cost effectiveness

One cost-utility analysis was identified that evaluated the relative cost effectiveness of percutaneous RFA versus a single alternative treatment — nephron-sparing surgery (NSS) — in 65-year-old male patients with small (<4 cm) RCC in the United States of America.

A decision-analytic Markov model with four states and a lifetime horizon following treatment was developed to estimate life expectancy and lifetime costs. The model included presence of RCC, treatment effectiveness and costs, and short- and long-term outcomes. The analysis adopted a quasi-societal perspective, whereby the costs of disease management were included, irrespective of who incurred them.

The study did not present clinical effectiveness data from clinical trials. A number of different data sources including a meta-analysis and published studies were used to estimate the probability of local recurrence and direct progression to metastatic disease following tumour treatment. The base-case analysis assumed that the yearly probability of local recurrence was 10% higher (relative difference) for RFA than for NSS, in the absence of studies directly comparing the effectiveness of RFA and NSS. This assumption was tested in the sensitivity analysis. The probability of direct progression to metastatic disease was assumed to be the same for both treatments. The model incorporated estimates of costs for RFA and NSS procedures, treatment and ongoing costs for local recurrence, computed tomographic (CT) surveillance costs and ongoing costs for metastatic disease.

Benefits were expressed as quality adjusted life years (QALYs). Due to a lack of studies providing data on both the utilities and the costs associated with the post-operative, post-procedure and metastatic RCC health states, these were derived from published studies reporting comparable states for colon cancer. The utility estimates were then scaled to reflect underlying age-specific quality of life, based on a published study. Both future costs and QALYs were discounted by 3%.

The results derived from the model showed the expected QALY gains were 9.682 and 9.689 per patient for RFA and NSS, respectively. The associated lifetime costs were $51,952 (approximately £32,513) for RFA and $59,941 (approximately £37,501) for NSS. Assuming a societal willingness-to-pay threshold of $75,000 (approximately £46,000) per QALY, RFA was the preferred strategy over NSS. This willingness-to-pay threshold is higher than that currently assumed for the UK of £30,000 per QALY, and this should therefore be considered with these results (note: all reported costs converted to GBP using the exchange rate as at 21 July 2011).
One-way sensitivity analyses were performed and showed that RFA remained the preferred strategy when the probability of recurrence post-RFA was up to 48% higher relative to NSS. RFA dominated NSS when the probability of local recurrence post-RFA was less than 0.4%. The results were sensitive to short-term RFA costs and NSS costs, and to post-NSS utilities. The results were robust to changes in the 1 month post-NSS utilities; short-term post-RFA utilities; the percentage of patients who underwent complete tumour ablation; costs and utilities for all long-term health states; the probability of developing metastatic disease; the probability of RCC-related death and CT costs. The sensitivity analyses were appropriate, however given the range of uncertainty in multiple parameters included in the model, probabilistic sensitivity analysis may have been more appropriate.

The limitations of the cost-utility analysis include some concerns about the methodological quality of the meta-analysis from which some values to populate the model were derived. In addition the quasi-societal perspective applied is broader than that of the NHS and social services perspective of interest in the UK, therefore potentially limiting the generalisability of the findings. The use of utilities for colon cancer was acceptable but not ideal. Finally, the authors note that the main limitation of RFA is that long-term outcomes are unknown, including RCC local recurrence rates and long-term survival.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The evidence note process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

For further information about the evidence note process, see www.healthcareimprovementscotland.org

To propose a topic for an evidence note, email evidencenotes.HCIS@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

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