National Institute for Health and Care Excellence

IP1031/3 Endoscopic bipolar radiofrequency ablation for malignant biliary obstruction

IPAC date: 12th September 2024

Com. no.	Consultee name and organisation	Sec. no.	Comments [sic]	Response
Agreement on the recommendations				
1.	Consultee 1 NHS Professional	General	No comments but I agree with the recommendations	Thank you for your comments.
2.	Consultee 2 NHS Professional	General	No comments but I agree with the recommendations	Thank you for your comments.
Disagreement on the recommendations				
3.	Consultee 3 Boston Scientific Corporation	1.1	Thank you for the opportunity to comment on these draft recommendations. We are disappointed to see that the draft recommendations have not changed despite the new evidence considered. We note that statistically significant longer overall survival (OS) times were demonstrated in 2 of the 3 RCTs with the largest number of patients as well as for a subgroup in the Meta Analysis. We are pleased to see that evidence suggests a trend in favour of RFA plus stent. We note that Gao 2021 showed that treatment with RFA was found to be an independent predictor of improved OS, that Yang 2018 found RFA to be the main predictive factor of survival and Xia 2021 reported median OS being statistically significantly longer in the RFA plus plastic stent group We note that whilst some studies evaluated in this assessment did not routinely find statistically significant differences in stent patency between RFA plus stent and stent only, at least 1 RCT did. (Yang	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation. The committee makes recommendations based on its assessment of the evidence on the efficacy and safety of that individual interventional procedure. The rationale behind the recommendations has been updated and is included in the guidance ('why the committee made these recommendations'). All the studies cited by the consultee are included in the overview.

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			2018, an RCT with low risk of bias in all domains, p=0.02). The Bayer et al (2023) HTA showed that primary RFA appears to be a beneficial adjunct to standard care and, as has been shown in other reviews, increases survival time as well as a reduction in the hazard of mortality by at least 45%. We recognise the potential benefit of further research into the use of RFA and stent patency however suggest that stent patency following use of RFA is not entirely without evidence from a peer reviewed and published journal. For this reason, given that surgical intervention is often not an option for these patients, we propose the current recommendation for "research only" be revised to permit the use of RFA in specialised centres of excellence under “Special Arrangements” This would maximise the opportunity for careful selection by clinicians of patients who have the potential to benefit from symptom relief and longer overall survival, as shown by studies contained in the draft guidance.	
4.	Consultee 3 Boston Scientific Corporation	1.2	BSC is aware that there is concern amongst the clinical community that, despite some clear evidence of patient benefit, if the recommendations remain unchanged (i.e. Research Only) then this technology will not be available as an option to treat patients. This is due to the fact that despite potential benefits, including significantly improved overall survival, existing centres will stop its use, given a Research Only recommendation. RFA has the potential to provide an option for treating strictures caused by cancer. As documented by Pancreatic Cancer UK people with pancreatic cancer commonly experience a range of complex and severe symptoms including pain, nausea, vomiting, bloating, reflux, altered bowel habits, fatigue, cachexia and psychological distress. In addition, the British Society of Gastroenterology Guidelines for the Diagnosis and Management of Patients with CCA	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation. Please see response to comment 3. The British Society of Gastroenterology (BSG) Guidelines are included in the 'existing assessments of this procedure' section of the overview. The committee considered the patient organisation submission and BSG

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			state that patients with CCA are reported to have lower measured physical and psychological health-related quality of life scores than controls as well as anxiety, depression and social isolation. It is disappointing that the draft guidance does not appear to have fully considered the impact of these types of cancer upon patent's lived experiences and that by recommending further research rather than its use in specialised centres of excellence under “Special Arrangements” then some patients who might benefit from RFA will not be able to benefit.	guidelines in their deliberations.
5.	Consultee 3 Boston Scientific Corporation	Why the committee made these recommendations	It is positive that of the 7 studies included in the evidence 5 were RCTs and 3 of these were assessed as being of low risk of bias. Overall Survival (OS) We note that statistically significant longer OS times were demonstrated in 2 of the 3 RCTs with the largest number of patients as well as for a subgroup in the Meta analysis. We are pleased to a trend in favour of RFA plus stent. We note that Gao 21 showed that treatment with RFA was found to be an independent predictor of improved OS, that Yang 2018 found RFA to be the main predictive factor of survival and Xia 2021 reported median OS being statistically significantly longer in the RFA plus plastic stent group. Whilst OS is only one of the outcome measures evaluated in this assessment, we would ask NICE to consider giving it a greater weighting in its decision about the recommendation it will make. This is due to the fact that for many patients increased survival time is a very important factor. For this reason, we would once again suggest that the recommendations are modified to “Special Arrangements” to allow some patients to be treated in specialised centres of excellence. Safety In addition to the data of overall survival, we would suggest that the	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation. The rationale section has been updated, please see response to comment 3. Section 3.7 has also been updated.

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			evidence related to safety is given greater recognition as we feel that the fact that overall postoperative adverse events were comparable between patients with RFA plus stent and people with stent only reinforces the role of RFA as a procedure with no increased risk and potential benefits such as longer overall survival. We are reassured that incidence of Cholangitis was generally comparable between the RFA plus stent groups and stent only groups. We note that 2 studies found statistically significantly higher incidence of acute cholecystitis in the RFA plus stent group vs the stent only group, but that not all studies supported this. We agree however that additional research into this complication would be beneficial. We are reassured that other reports of complications such as pancreatitis, bleeding, perforation, liver abscess were low in numbers and not statistically significantly different between RFA plus stent and stent only procedures. Given that NICE's IPG "Special Arrangements" category is used when there is uncertainty about whether a procedure is safe or effective, and the data supports RFA safety and some effectiveness, we would like to ask that this the recommendation for this guidance is recategorised to Special Arrangements.	
6.	Consultee 3 Boston Scientific Corporation	1.1	We agree that regrettably for many patients diagnosed with biliary obstruction caused by cancer suffer significant unpleasant symptoms, and that surgical resection is often not possible. We also recognise that stents are frequently blocked due to tumour growth. Whilst studies evaluated in this assessment did not routinely find statistically significant differences in stent patency between RFA plus stent and stent only, at least 1 RCT did (Yang 2018, an RCT with low risk of bias in all domains, did p=0.02). Therefore, whilst we recognise the potential benefit of further research into the use of RFA and stent patency we would suggest that stent patency	Thank you for your comment. Although Yang (2018) showed improvement in stent patency, people in this study received more RFA sessions and had their stent replaced more frequently than people in other studies. Also, no benefit in stent patency was illustrated in other key evidence included in the overview.

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			following use of RFA is not entirely without evidence from a peer reviewed and published journal. For this reason, given that surgical intervention is often not an option for these patients, then we propose the current recommendation for "Research Only" be revised to permit the use of RFA in specialised centres of excellence under “Special Arrangements”. We feel this would maximise the opportunity for careful selection by clinicians of patients who have the potential to benefit from symptom relief and longer overall survival, as shown by studies contained in the draft guidance. We are aware that there is some concern amongst the clinical community that, despite some clear evidence of patient benefit, if the recommendations remain unchanged then this technology will not be available as an option to treat patients. This is due to the fact that despite potential benefits, including significantly improved overall survival, existing centres will stop its use (given a Research Only recommendation).	The committee has considered this comment but decided not to change the recommendation. Please see response to comment 3.
7.	Consultee 3 Boston Scientific Corporation	1.1	We agree that RFA has the potential to provide an option for treating strictures caused by cancer. As documented by Pancreatic Cancer UK people with pancreatic cancer commonly experience a range of complex and severe symptoms including pain, nausea, vomiting, bloating, reflux, altered bowel habits, fatigue, cachexia and psychological distress. In addition, the British Society of Gastroenterology Guidelines for the Diagnosis and Management of Patients with CCA state that patients with CCA are reported to have lower measured physical and psychological health-related quality of life scores than controls as well as anxiety, depression and social isolation. We are disappointed that the draft guidance does not appear to have taken the impact of these types of cancer upon patient's lived experiences and that by recommending further research rather than its use in specialised centres of excellence under “Special Arrangements” then some patients who might benefit from RFA will	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation. Please see response to comment 3. Also, section 3.7 has been updated, noting there is a lack of evidence showing that this procedure improves quality of life.

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			not do so. As higher and statistically significant Karnofsky Performance Status measures were demonstrated in patients who had undergone RFA (Gao 2021 and Yang 2018) we would ask that greater weight, than is currently the case, is given to the potential to improve patients' functional performance as this is likely to impact upon their quality of life.	
8.	Consultee 3 Boston Scientific Corporation	1.1	We are pleased to see that the Bayer et al (2023) HTA showed that primary RFA appears to be a beneficial adjunct to standard care and, as has been shown in other reviews, increases survival time as well as a reduction in the hazard of mortality by at least 45%. In addition, the lack of evidence for RFA increasing two of the most common adverse events reinforce the findings in NICE's evaluation that RFA does not appear to increase the potential for patient harm. We feel that these factors are supportive of our suggestion that the Committee should consider changing its recommendations to "Special Arrangements" so that patients who are unable to benefit from surgical intervention may be given the option of RFA in specialised centres of excellence. We would like to draw the Committee's attention to a paper published in Nature in 2022 by Gonzalez-Carmona et al (https://doi.org/10.1038/s41598-021-04297-2). Using retrospective analysis of all patients diagnosed with non-curative resectable biopsy-proven extrahepatic cholangiocarcinoma over a 10 year period, up to 2020, the impact of regular additional RFA on the survival of patients who were also receiving systemic chemotherapy was assessed. This study evaluated overall survival, progression free survival and toxicity using univariate and multivariate approaches. Patients who received combined RFA and systemic chemotherapy had significantly longer median overall survival (17.3 vs. 8.6 months, p = 0.004) and progression free survival (12.9 vs. 5.7 months, p = 0.045) compared to the systemic chemotherapy only group.	Thank you for your comment. Bayer et al. (2023) is included in the 'existing assessments of this procedure' section of the overview, and the committee considered it in their deliberations. Gonzalez-Carmona et al. (2022) has been added to the appendix. The committee has considered this additional information but decided not to change the recommendation.

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			These findings were despite the fact that the mean MELD (model for end stage liver disease) was even higher (10.1 vs. 6.7, p = 0.015) in the RFA + systemic chemotherapy group. As has been seen in other studies, therapy-related cholangitis occurred more often in the combined treatment group (p = 0.031). We feel that this paper contributes further data showing the potential, and significant, survival benefits for patients who are treated with RFA in addition to standard approaches to care Whilst we recognise that further evidence should be generated, including around stent patency and quality of life, we feel that the conclusions reached by Bayer et al, Gonzalez-Carmona et al, and data presented in NICE's own evaluation, are consistent with the NICE's IPG definition of "Special Arrangements" and it is for this reason that we request a change in the recommendation, from "Research Only" to "Special Arrangements".	
Comments relating to committee comments				
9.	Consultee 3 Boston Scientific Corporation	3.7	As higher and statistically significant Karnofsky Performance Status measures were demonstrated in patients who had undergone RFA (Gao 2021 and Yang 2018) we would ask that greater weight than is currently the case, is given to the potential to improve patients' functional performance as this is likely to impact upon their quality of life.	Thank you for your comment. Section 3.7 has been updated, noting that there is a lack of evidence showing that this procedure improves quality of life.
10	Consultee 3 Boston Scientific Corporation	3.8	Gonzalez-Carmona et al 2022, report a retrospective analysis of patients diagnosed with non-curative resectable biopsy-proven extrahepatic cholangiocarcinoma over a 10 year period, up to 2020, looking at the impact of regular additional RFA on the survival of patients who were also receiving systemic chemotherapy. This study evaluated overall survival, progression free survival and toxicity using univariate and multivariate approaches. Patients who received combined RFA and systemic chemotherapy had significantly longer median overall survival (17.3 vs. 8.6 months, p = 0.004) and progression free survival (12.9 vs. 5.7 months, p =	Thank you for your comment. Gonzalez Carmona et al. (2022) has been added to the appendix of the overview. The committee has considered this additional information but decided not to change the recommendation.

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			0.045) compared to the systemic chemotherapy only group. These findings were despite the fact that the mean MELD (model for end stage liver disease) was even higher (10.1 vs. 6.7, p = 0.015) in the RFA + systemic chemotherapy group. As has been seen in other studies therapy-related cholangitis occurred more often in the combined treatment group (p = 0.031). We feel that this paper contributes further data showing the potential, and significant, survival benefits for patients who are treated with RFA in addition to standard approaches to care. (Ref: Gonzalez-Carmona et al. Impact of regular additional endobiliary radiofrequency ablation on survival of patients with advanced extrahepatic cholangiocarcinoma under systemic chemotherapy. Nature. 2022)	

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