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REVIEW ARTICLE

Cryotherapy – a mature ablation technique

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Abstract
This article discusses the use of cryotherapy for the treatment of hepatic tumours, from its early origins to the present day. Results of therapy, preoperative assessment, safety, and the pros and cons of its use are described.

Introduction

Cryotherapy is a rather more mature ablative technique than radiofrequency ablation (RFA), and was started in earnest using coaxial insulated probes under ultrasound control by a few groups in the late 1980s [1]. However, its origins stem back over one and a half centuries to Arnott [2], when it was used as a means of local pain control and haemostasis in cancer.

Over 2100 patients had received hepatic cryotherapy in a world survey conducted in 1999 [3], with the largest response from the United States. Our own experience over the last 12 years is 172 patients treated with hepatic cryotherapy. This time and effort should now provide us with some useful data with which to measure its value.

Applications and results

The use of cryotherapy to completely ablate unresectable liver metastases is perhaps the central issue regarding its role in the surgeon's tool box. Our definition of unresectable lesions encompasses multiple (more than five lesions) bilobar disease that is beyond the scope of multiple segmental resections to achieve total clearance.

We recently reported long-term survival data from our series of 146 patients following cryotherapy with or without resection, for colorectal metastases. At 1, 2, 3, 4 and 5 years survival rates were 89%, 65%, 41%, 24% and 19%, respectively. Perhaps the most fundamental issue was that 25% of patients with six or seven lesions, who might not have been offered this option by many groups, were alive at 5 years (Table I) [4]. The use of cryotherapy is not, in this group's view, a palliative procedure: the aim of the therapy is complete tumour eradication with at least 1 cm clearance, which we have achieved in 78% of patients. Other units have similarly reported the marked difference in survival in those patients in whom complete tumour ablation was achieved [5–7].

Standard preoperative assessment of patients includes computed tomography (CT) scans of the chest, abdomen and pelvis, and bone scan. This is followed by CT portography in patients in whom extrahepatic disease is excluded.

The number of lesions clearly must be of some importance, but in the select group of patients with no extrahepatic disease and where we were successful in completely destroying all liver disease, the number of hepatic lesions was not prognostic.

However, the diameter of lesions is highly prognostic for local recurrence, and our disappointing early results with lesions >3 cm led to a change in our approach to resect larger lesions wherever possible, which has already resulted in a much lower local recurrence rate. Both preoperataive and postoperative carcinoembryonic antigen (CEA) levels are also highly prognostic for long-term survival. In our series, raised postoperative CEA was highly prognostic for disease-free intervals of the cryotherapy sites, the remaining liver, and the extrahepatic sites, as well as overall disease-free interval [4].

While this group would still not advocate cryotherapy for resectable disease in a non-cirrhotic liver, the

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Table I. Survival figures for cryotherapy of liver lesions demonstrating comparable survival for cryotherapy used with liver resection and the importance of completeness of ablation [4].

Operation type	Number of patients	Survival rate (%)				
		1-year	2-year	3-year	4-year	5-year
Cryotherapy alone	92	85	57	32	21	13
Cryotherapy and liver resection	80	85	66	42	19	19
Number of cryotreated lesions						
1–2	97	87	61	38	21	17
3–6	66	85	62	33	17	11
7–9	9	67	44	33	33	22
Completeness of ablation						
Yes	146	89	65	41	24	19
No	26	65	38	13	8	0

randomized trial by Korpan [8] suggests that quite similar survival results may be achieved. The 3-, 5- and 10-year survival rates for the cryotherapy group were 60%, 44% and 10%, respectively, whereas those for the resection group were 51%, 36% and 5%, respectively. Despite being strong proponents of cryotherapy, we do not believe that the operative mortality rates of cryotherapy and liver resection are different.

The safety of cryotherapy compared with RFA is a controversial issue, clouded by the fact that many RFA series have been done percutaneously, and almost all cryotherapy is done at open laparotomy. If one compares mortality and morbidity of cryotherapy and RFA there is little difference [3,9,10]. Intraoperative ultrasound is essential for cryotherapy and RFA, whatever access route is used. Numerous studies have demonstrated that intraoperative ultrasound is capable of identifying hepatic lesions that are undetectable by preoperative imaging [11,12] or palpation of the liver itself [13]. The benefit of an open operation is that the surgeon has the critical advantage of mobilizing the liver and feeling and seeing lesions in addition to using high frequency ultrasound, greatly assisting the placement of RFA probes or cryoprobes.

There is clear evidence from some series that the recurrence rate after open RFA is much lower than after percutaneous RFA. In a study comparing open, percutaneous and laparoscopic RFA, with a median follow-up of 12 months, Kuvshinoff and Ota reported ablation site recurrence in only 6% of open procedures [14]. Laparoscopic and percutaneous RFA had more deleterious local recurrence rates: 23% and 53%, respectively.

In patients with six or seven lesions in whom we have reported a 25% 5-year survival, we wonder how many of these could have been treated by percutaneous RFA. Of course with such a large number of lesions being treated with cryotherapy, even with multiple probe placement, duration of these procedures is also an issue and RFA would be much slower. We have used cryotherapy to treat the contralateral side of the liver at the time of resection, and reported no difference in survival compared to resection alone at 3 years in 117 patients [15]. Our patients who have had cryotherapy at the time of their resection currently have a 30% 5-year survival.

We have used cryotherapy to treat an involved or close (<1 cm) edge of resection margins for colorectal metastases in 110 patients. At a median follow-up of 70.43 months, 49 patients (66%) had liver recurrence, with only 8 patients with local edge recurrence following edge cryotherapy [16]. The median survival for patients with an involved margin was 32.3 months and for a close margin was 39.3 months. The demonstration of a 5-year survival of 25% in patients with an involved resection margin is significant in these patients, in that they would have been expected to die of their inadequate resection.

The pros and cons of cryotherapy

Cryotherapy has some clear advantages over other common local ablative techniques. First, multiple probes can be used concurrently, which is important for limiting the time of these procedures. Unipolar RFA systems simply cannot use multiple probes simultaneously, although bipolar probes might be able to do so in the future. The most important difference between RFA and cryotherapy, at least in our health system, is that cryoprobes can be re-sterilized and used for many years. We believe that the ability to feel, image and accurately place probes in lesions is considerably easier at open operation. The edges of cryoablated lesions are very clearly demarcated from normal tissue on ultrasound, and allow for continuous monitoring of the iceball if necessary.

The disadvantages of cryotherapy include the diameter of probes (minimum 3.5 mm for a liquid nitrogen system), which essentially precludes percutaneous use. Cracking of cryolesions does occur frequently, accounting for 8% of cryotherapy-associated morbidity [3], and can cause considerable bleeding. We control this quite easily with

compression and a figure-of-eight suture if needed. More substantial haemorrhage is uncommon and is more usually associated with incomplete thawing of the cryolesion prior to closing the abdomen. However, the subsequent postoperative bleeding from this and other causes following cryotherapy is comparable to that of liver resection.

Cryoshock is a cytokine-mediated complication characterized by varying degrees of severe coagulopathy, disseminated intravascular coagulation (DIC) and multi-organ failure. It is causally associated with complete thaw prior to refreezing and double freeze cycles [17], as well as volume of cryotherapy. The underlying mechanism of cryoshock has not been completely elucidated, although it appears to be related to post-cryotherapy circulating inflammatory mediators, of which interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are the most important [18].

As previously mentioned, we practise a partial double freeze thaw process and as such have not lost a patient to cryoshock [3], although the world literature indicates that cryoshock affects 1% of cryotherapy patients.

Conclusions

Since its implementation, cryotherapy has matured in a number of ways and as a result we have changed aspects of our use of cryotherapy for liver lesions. The most pertinent of these changes are listed below.

1. Only complete cryotherapy offers long-term survival. We have demonstrated on numerous occasions that incomplete cryotherapy greatly affects the potential benefit that can be achieved.
2. The best results for cryotherapy consistently seem to be for lesions ≤ 3 cm in diameter.
3. Intraoperative ultrasound would be advocated by our department as a means of assessing cryotherapy margins in real time.
4. The Pringle manoeuvre during cryotherapy effects a more rapid and thorough iceball, especially when the lesion is adjacent to large vessels.
5. The utilization of a partial double freeze thaw technique instead of the previously described complete double freeze thaw, might confer a safety benefit without any appreciable loss in efficacy.

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