Chapter 12
Minimally Invasive Intraluminal Tumor Ablation

Patrick F. Forde, Michael G. Bourke, Slawomir Salwa, Gerald C. O'Sullivan, and Declan M. Soden

Abstract Surgery is the standard modality for the removal of tumors, either alone or in combination with other therapies such as radiotherapy and chemotherapy. These treatment adjuncts can be associated with significant toxicity, may not be appropriate at the time of diagnosis, and do not necessarily reduce the risk of metastasis. Consequently, a considerable volume of research has focused on the identification, validation, and refinement of alternative approaches and therapies. Here we outline a novel treatment for intraluminal tumors via an endoscopic device that delivers an electroporating pulse, resulting in enhanced tumor-targeted therapeutic absorption. This device has been demonstrated to be highly effective in the curative treatment of canine intraluminal tumors and has also been demonstrated to successfully deliver DNA in a targeted manner to intraluminal porcine tissues.

Keywords Electroporation • EndoVe • Electrochemotherapy • Gene therapy • Gastrointestinal cancers

Background

Removal of the primary tumor mass remains a critically important element in the treatment of solid malignant tumors, as it has the potential to significantly relieve symptoms, forestall complications, and facilitate responsiveness to multimodal systemic therapies [1–4]. However, many cancers are resistant to current multimodal treatment regimens, creating a need for therapeutic innovations and discovery. The causes of this intractability may include advanced stage disease at presentation, which limits the application or effectiveness of treatments, resistance of tumor cells to chemotherapy or radiation therapy, anatomical locations of the cancer which preclude either complete excision or ablation by radiotherapy, and the presence of inter-current illnesses, which may limit therapeutic options or adversely affect the risks and benefits of treatment [1, 5–7]. Poor quality of life and the intrusion on their valuable remaining time resulting from invasive or toxic therapies are a major problem for many patients with incurable tumors [8–10]. In this context, an ideal cancer treatment should effectively control local disease, be applicable to a diversity of tumor types

D.M. Soden (✉)
Cork Cancer Research Centre, Leslie C. Quick Jnr. Laboratory, BioSciences Institute, University College Cork, Cork, Ireland
e-mail: d.soden@ucc.ie

S.T. Kee et al. (eds.), *Clinical Aspects of Electroporation*,
DOI 10.1007/978-1-4419-8363-3_12,

and anatomical locations, be effective against locally recurrent disease, facilitate multimodal and systemic therapies, be minimally intrusive, and improve patient well-being and life expectancy by tumor control or cure.

Electroporation

Electroporation makes use of an externally applied electric field to increase the permeability of plasma membranes, thus achieving highly efficient gene and/or drug transfer [11–15]. Through a variety of processes, electroporation temporarily disrupts membrane stability, causing pores to form within the membrane. With careful control of the electric field strength and the duration of the cell's exposure to it, these pores reseal after a short period of time [11]. Many chemotherapeutic drugs, including bleomycin and cisplatin, are poorly permeant at the cell membrane under physiologic conditions. Electropermeabilization therefore offers a novel means of increasing delivery of these drugs into cancer cells, with a consequent improvement in antitumor effect [13, 15–17]. This approach is known as electrochemotherapy. Now that the efficacy, safety, and clinical utility of electrochemotherapy have been established for skin-based tumors, there is continued impetus to modify and further develop the clinical potential of this technology.

Endoscopic Electroporation with the EndoVe Device

Minimally Invasive Procedures

There are many advantages to the use of minimally invasive surgical options, including reduced pain, a frequently reduced hospital stay, a more rapid return to normal activity, and, in the case of gastrointestinal surgery, reduced ileus [18–21]. Used appropriately, minimally invasive techniques therefore have the potential to lead to an overall improved standard of patient care.

In the context of malignant disease, several minimally invasive techniques have been developed, employing a range of energy-based methods for in situ tumor destruction. These include targeted radiofrequency ablation, laser ablation, cryoablation, photodynamic therapy, high-intensity focused ultrasound (HIFU), and techniques that allow for enhanced targeting of radiotherapy [22–31]. Oncologic surgical principles require that neoplastic tissue is excised with a margin sufficient to ensure tumor clearance. If a minimally invasive technique employing an energy-based treatment can destroy equivalent neoplastic tissue volumes with an equivalent margin of normal tissue, then the outcome in terms of disease-free survival should be at least equal to that following conventional open surgery. However, the benefits associated with the use of minimally invasive techniques set them apart, as there is the potential to achieve similar outcomes of patient survival but with reduced treatment-associated morbidity.

The Endoscopic Electrode: EndoVe

The ability to localize and treat internal cancerous tissue with electrochemotherapy, without disrupting nontarget tissues or their physiological function, presents a number of challenges.

Overcoming these requires both a means of delivering chemotherapeutic agents specifically to the diseased tissue and the development of minimally invasive options to facilitate targeted pulse delivery.

The available technology for delivery of electrochemotherapy has to date been reliant on macroelectrodes, such as calipers and needles, thus limiting its application to surface tumors. Efficient and safe electroporation of internal cancers, especially luminal tumors, have therefore not been possible thus far. However, electrode modification raises the potential for endoscopic, laparoscopic, or image-guided delivery of electric current to more deep-seated internal tumors [17]. For example, were it possible to deliver permeabilizing electric pulses to intra-abdominal, intra-thoracic, or genitourinary tumors, many lesions that have previously been deemed inoperable would be amenable to treatment with electrochemotherapy. It is also likely that electrode modification would allow electrochemotherapy to treat many, currently inoperable or incurable, primary cancers with curative intent. In particular, cancers of the foregut and bladder, which are often either incurable at presentation or unsuitable for conventional therapies due to a lack of patient fitness, are often readily accessible to endoscopes, making them ideal targets for electrochemotherapy delivered via an endoscopic device. Electrochemotherapy could also be added to many current systemic multidrug chemotherapy regimens to improve their efficacy. Similarly, electrochemotherapy could also be applied to sensitize recalcitrant cancers to radiation therapy, thus allowing a more targeted tumoricidal therapy with less collateral tissue injury. The EndoVe device has been developed to deliver electroporation endoluminally.

The EndoVe was designed using principles common to all electroporation devices; however, it fits on the end of a conventional endoscope, thereby allowing both direct tumor visualization and targeting. It has a flexible end, which attaches to the endoscope but also sits apart from it, in order to maximize luminal visualization (Fig. 12.1). The creation of a vacuum effect draws tissue into a chamber within the EndoVe, thus bringing the tumor into contact with plate electrodes contained within this chamber, allowing for electric field application. This chamber, which has a transparent

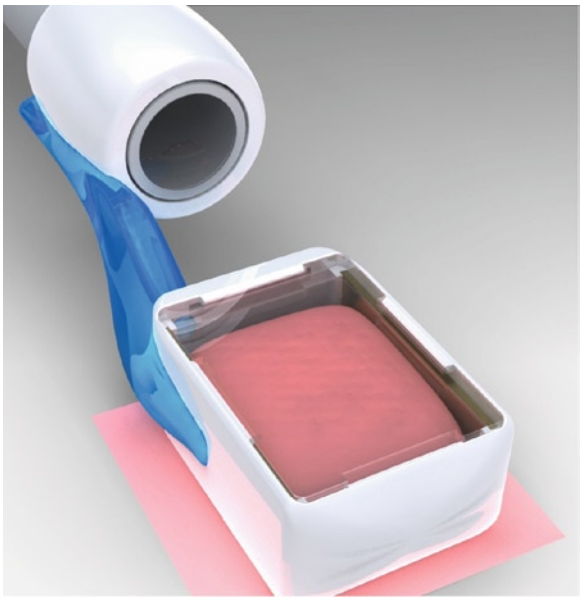

Fig. 12.1 EndoVe device which attaches to the end of an endoscope

roof that allows for tissue capture to be confirmed visually, also facilitates targeted drug delivery. The design and size of the chamber can be altered based on tumor size and location to allow for optimum tumor accessibility and tumor-electrode contact.

The EndoVe has already been applied to the treatment of tumors in small and large animals, and has been approved for a phase 1 clinical trial. It also has the potential to deliver gene therapy to nonskin-based tumors and to deliver both anticancer drugs and genes in either the adjuvant or neoadjuvant setting.

Preclinical Case Study

A 14-year-old Scottie terrier was brought to a local veterinary surgeon with per rectum bleeding and loss of condition, including significant recent weight loss. Colonoscopy revealed a nonobstructing, 5 cm long, circumferential rectal tumor, situated approximately 3 cm from the anal margin (Fig. 12.2a). Histopathological analysis determined that this lesion was a moderately differentiated rectal adenocarcinoma. The tumor was deemed unsuitable for surgical resection and the dog was referred for electrochemotherapy. Bleomycin was delivered intravenously. Using successive EndoVe applications, the entire lesion was treated with electrochemotherapy. Follow-up colonoscopy 5 weeks following treatment demonstrated significant regression of the tumor, in association with a marked improvement in the dog's clinical condition (Fig. 12.2b).

Conclusion

Electrochemotherapy is an effective drug delivery system, which acts by greatly enhancing the local cytotoxicity of the chemotherapeutic drug. The advantages of this therapy are its simplicity, the short duration of treatment sessions, with an associated reduction in anesthetic requirements, reduced chemotherapeutic dosages, the comparatively low costs, its minimal side effects, as well as the potential for a significantly reduced in-hospital stay, both before and after treatment. With the development of endoscopic delivery systems, such as the EndoVe, electrochemotherapy could increasingly be applied to a diversity of internal cancers as a minimally invasive tumor ablation procedure.

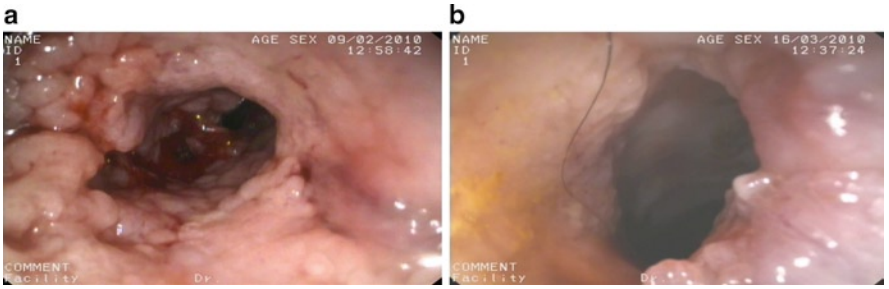

Fig. 12.2 Preclinical electrochemotherapy of a rectal adenocarcinoma. (**a**) Before treatment. (**b**) Five weeks after treatment

References

1. Termuhlen PM, Kemeny MM. Surgery in the older patient. Oncology (Williston Park) 2002;16(2):183–9; discussion 194–6, 199.
2. Easson AM, Asch M, Swallow CJ. Palliative general surgical procedures. Surg Oncol Clin N Am. 2001;10(1):161–84.
3. Shi Y, Zhou Y. The role of surgery in the treatment of gastric cancer. J Surg Oncol. 2010;101(8):687–92.
4. Wasserberg N, Kaufman HS. Palliation of colorectal cancer. Surg Oncol. 2007;16(4):299–310.
5. Weichselbaum RR, Dahlberg W, Little JB. Inherently radioresistant cells exist in some human tumors. Proc Natl Acad Sci USA. 1985;82(14):4732–5.
6. Voltz E, Gronemeyer H. A new era of cancer therapy: cancer cell targeted therapies are coming of age. Int J Biochem Cell Biol. 2008;40(1):1–8.
7. Kreeft A et al. The surgical dilemma of 'functional inoperability' in oral and oropharyngeal cancer: current consensus on operability with regard to functional results. Clin Otolaryngol. 2009;34(2):140–6.
8. McLarnon C et al. Quality-of-life considerations in treatment of unresectable, recurrent head and neck cancer. Expert Rev Anticancer Ther. 2010;10(3):345–52.
9. Mastracci TM et al. The impact of surgery for colorectal cancer on quality of life and functional status in the elderly. Dis Colon Rectum. 2006;49(12):1878–84.
10. Gunnars B, Nygren P, Glimelius B. Assessment of quality of life during chemotherapy. Acta Oncol. 2001;40(2–3):175–84.
11. Tsong TY. Electroporation of cell membranes. Biophys J. 1991;60(2):297–306.
12. Somiari S et al. Theory and *in vivo* application of electroporative gene delivery. Mol Ther. 2000;2(3):178–87.
13. Sadadcharam M, Soden DM, O'Sullivan GC. Electrochemotherapy: an emerging cancer treatment. Int J Hyperthermia. 2008;24(3):263–73.
14. Jaroszeski MJ et al. *In vivo* gene delivery by electroporation. Adv Drug Deliv Rev. 1999;35(1):131–7.
15. Heller R, Gilbert R, Jaroszeski MJ. Clinical applications of electrochemotherapy. Adv Drug Deliv Rev. 1999;35(1):119–29.
16. Larkin JO et al. Electrochemotherapy: aspects of preclinical development and early clinical experience. Ann Surg. 2007;245(3):469–79.
17. Soden DM et al. Successful application of targeted electrochemotherapy using novel flexible electrodes and low dose bleomycin to solid tumours. Cancer Lett. 2006;232(2):300–10.
18. Choh MS, Madura JA, II. The role of minimally invasive treatments in surgical oncology. Surg Clin North Am. 2009;89(1):53–77, viii.
19. Greene FL et al. Minimal access cancer management. CA Cancer J Clin. 2007;57(3):130–46.
20. Greene FL. Minimal access surgery alters approach to cancer. J Surg Oncol. 2007;95(4):276–7.
21. Robinson TN, Stiegmann GV. Minimally invasive surgery. Endoscopy. 2004;36(1):48–51.
22. Kennedy JE. High-intensity focused ultrasound in the treatment of solid tumours. Nat Rev Cancer. 2005;5(4):321–7.
23. Curley SA et al. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg. 2000;232(3):381–91.
24. Zlotta AR et al. Percutaneous transperineal radiofrequency ablation of prostate tumour: safety, feasibility and pathological effects on human prostate cancer. Br J Urol. 1998;81(2):265–75.
25. Posteraro AF, Dupuy DE, Mayo-Smith WW. Radiofrequency ablation of bony metastatic disease. Clin Radiol. 2004;59(9):803–11.
26. Robertson CA, Evans DH, Abrahamse H. Photodynamic therapy (PDT): a short review on cellular mechanisms and cancer research applications for PDT. J Photochem Photobiol B. 2009;96(1):1–8.
27. Zhou XD et al. The role of cryosurgery in the treatment of hepatic cancer: a report of 113 cases. J Cancer Res Clin Oncol. 1993;120(1–2):100–2.
28. Lezoche E, et al. Ultrasound-guided laparoscopic cryoablation of hepatic tumors: preliminary report. World J Surg. 1998;22(8):829–35; discussion 835–6.
29. Chung DE, Te AE. High-power 532 nm laser prostatectomy: an update. Curr Opin Urol. 2010;20(1):13–9.
30. Grant DG et al. Transoral laser microsurgery for early laryngeal cancer. Expert Rev Anticancer Ther. 2010;10(3):331–8.
31. Moran MS, Haffty BG. Radiation techniques and toxicities for locally advanced breast cancer. Semin Radiat Oncol. 2009;19(4):244–55.