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REVIEW ARTICLE

Focal therapies for the treatment of localized prostate cancer: The role of irreversible electroporation – Present or future?

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Abstract In the PSA era, the incidence of localized prostate cancer has been increasing. This reality requires new therapeutic strategies, in order to give an answer to patients, in whom active surveillance may be indicate but desire more interventionist strategy with minimal side effects and without compromising cancer control. In these cases, focal therapies that include irreversible electroporation may be effective alternative strategies. The irreversible electroporation is an emergent approach on focal treatment of localized PCa. The nonthermal mechanism that preserves the tissue architecture without damaging tissue structures, such as vessels and nerves within the target region, is the main advantage comparatively to other techniques used in focal treatment. The number of clinical studies is reduced and the results still immature.

PALAVRAS-CHAVE
Carcinoma da próstata;
Terapêutica focal;
Tratamento focal;
Eletroporação

Terapêuticas focais no tratamento do carcinoma da próstata localizado: o papel da eletroporação irreversível – presente ou futuro?

Resumo Na era do PSA, a incidência do carcinoma da próstata localizado tem vindo a aumentar. Esta realidade exige novas estratégias terapêuticas, a fim de poder dar uma resposta aos pacientes, os quais, embora esteja indicada a vigilância ativa, desejam uma estratégia mais interventiva com poucos efeitos adversos e sem compromisso do controlo da doença.

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Nestes casos, as terapêuticas focais, que incluem a eletroporação irreversível, podem ser uma estratégia alternativa efetiva. A eletroporação irreversível constitui uma abordagem emergente no tratamento do carcinoma da próstata localizado. O mecanismo de lesão celular não-térmico que preserva a arquitetura tecidular sem lesão de estruturas, tais como vasos e nervos dentro da região alvo, constitui a principal vantagem comparativamente com as outras técnicas utilizadas no tratamento focal. O número de estudos clínicos é reduzido e os resultados ainda são imaturos.

Introduction

In industrialized countries, the prostate cancer (PCa) is the most common cancer among men over 50 years.[1] The incidence is highest in Northern and Western Europe (>200/100,000), while rates in Eastern and Southern Europe have showed a continuous increase and appear to be reaching the levels seen in Northern and Western Europe.[2] Although the incidence has increased in all parts of Europe, this phenomenon is most notable in Northern Europe and in the youngest group (35–64 years).[2]

PCa is currently diagnosed in 15–20% of men during their lifetime, but the lifetime risk of death from PCa is only 3%.[3] The mortality attributable to this pathology tends to range widely from country to country in the industrialized world.[3] In most Western countries, mortality rates due to PCa have been decreasing, with varying rates across the different nations.[4] In Europe, during last decade, the 5-year relative survival percentages for prostate cancer steadily increased from 73.4% in 1999–2001 to 83.4% in 2005–2007, despite having identified discrepancies between countries of Eastern Europe and the rest of Europe.[5] Likewise, the United States of America has recorded a similar trend in mortality, condition for which aggressive PCa screening policy has had a preponderant role.[4]

Currently, PCa screening using PSA has contributed to the increasing the number of cases diagnosed at an earlier stage. Together with the improvement of imaging techniques and biopsy,[1] the incidence of localized, small volume and low grade PCa has increased substantially.[6] In these cases, active surveillance appears to be a feasible management strategy in carefully selected patients. However, 18% of men on active surveillance choose a radical approach due to anxiety.[3] On the other hand, despite technological progress in surgery and radiotherapy, the occurrence of side effects remains considerably high.[6]

Although in experimental phase, focal therapy using the most diverse techniques has gained preponderance by minimizing damages on the remaining gland and surrounding structures, while retaining the therapeutic benefits[6] and without commitment of the life expectancy.[7] This strategy is an approach similar to that already done in the treatment of solid-organ malignancies, such renal, thyroid, breast, liver and pancreas.[6]

There is evidence that the natural history of the disease is mainly driven by a lesion of large size and high grade called index lesion,[6] justifying this approach.

The high intensity focused ultrasound (HIFU) and cryotherapy are the most studied techniques. Others, such as photothermal laser, photodynamic therapy and focal brachytherapy, have been studied as plausible approaches to partial ablation of the prostate gland. Recently, irreversible electroporation (IE) appears to be a technique with enough potential to focal treatment of PCa.

Materials and methods

A literature search was done on PubMed and ScienceDirect databases using the keywords ''prostate cancer'', ''prostatic neoplasms'', ''focal treatment'', ''focal therapy'', ''irreversible electroporation''. The articles included were published between 01/01/2004 and 31/12/2014. Original articles, review articles and clinical trials conducted in humans were included. In each study, the following data were extracted: characteristics of target population, disease control outcomes, side effects and preservation of urinary continence and erectile function after treatment.

Irreversible electroporation

Principles and clinical applicability

The IE, used in the food industry for sterilization, emerged as a new method for minimally invasive tumour ablation.[8] The bases that have contributed to this evolution naturally derived of reversible electroporation, which has been used mainly as a research tool in the medical field to promote the transmembrane transport of genes, antibodies, RNA, DNA, and even drugs (e.g.: cytostatics).[8–10] Then, an electrical field that transiently increases the porosity of the membrane facilitates the exchange of substances.[8] In contrast, in IE an electrical field of much higher voltage is applied, which leads to permanent nanopore formation in the cell membrane, with disruption of cellular homeostasis and, consequently, cell death by apoptosis.[8,9,11,12] The dead cells are removed by the immune system and replaced through mechanisms of innate cellular regeneration. The preservation of the surrounding tissue architecture allows fast activation