BMJ Open

Machine learning in predicting extracapsular extension (ECE) of prostate cancer with MRI: a protocol for a systematic literature review

Adalgisa Guerra [1], Eduardo Negrão [2], Nickolaos Papanikolaou [3], Helena Donato [4]

To cite: Guerra A, Negrão E, Papanikolaou N, *et al*. Machine learning in predicting extracapsular extension (ECE) of prostate cancer with MRI: a protocol for a systematic literature review. *BMJ Open* 2022;**12**:e052342. doi:10.1136/bmjopen-2021-052342

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052342).

Received 21 May 2021
Accepted 12 March 2022

Check for updates

[1]Radiology, Hospital da Luz, Lisboa, Portugal
[2]Radiology, Centro Hospitalar Universitário de São João, Porto, Portugal
[3]Radiology, Royal Marsden Hospital NHS Trust, London, UK
[4]Documentation and Information Service, Centro Hospitalar e Universitario de Coimbra EPE, Coimbra, Portugal

Correspondence to
Dr Adalgisa Guerra; gisaguerra@gmail.com

ABSTRACT

Introduction In patients with prostate cancer (PCa), the detection of extracapsular extension (ECE) and seminal vesicle invasion is not only important for selecting the appropriate therapy but also for preoperative planning and patient prognosis. It is of paramount importance to stage PCa correctly before surgery, in order to achieve better surgical and outcome results. Over the last years, MRI has been incorporated in the classical prostate staging nomograms with clinical improvement accuracy in detecting ECE, but with variability between studies and radiologist's experience.

Methods and analysis The research question, based on patient, index test, comparator, outcome and study design criteria, was the following: what is the diagnostic performance of artificial intelligence algorithms for predicting ECE in PCa patients, when compared with that of histopathological results after radical prostatectomy. To answer this question, we will use databases (EMBASE, PUBMED, Web of Science and CENTRAL) to search for the different studies published in the literature and we use the QUADA tool to evaluate the quality of the research selection.

Ethics and dissemination This systematic review does not require ethical approval. The results will be disseminated through publication in a peer-review journal, as a chapter of a doctoral thesis and through presentations at national and international conferences.

PROSPERO registration number CRD42020215671.

Strengths and limitations of this study

- ⇒ To our knowledge, this is the first systematic review that aims to comprehensively synthesise the available evidence about the diagnostic performance of artificial intelligence (AI) and machine learning algorithms in predicting extra-capsular extension (ECE) in patients with prostate cancer.
- ⇒ This protocol has been developed following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols and has been registered with the International Prospective Register of Systematic Reviews.
- ⇒ We will include all studies with MRI criteria and AI models to detect ECE on pathology, excluding cross-sectional studies, case series, case reports, case–control studies, systematic reviews, conference proceedings and masters or PhD thesis.
- ⇒ The novelty of AI in the field of radiology, specially in the field of MRI for the diagnosis and staging of prostate cancer, and also the lack of robust studies with great number of cases, may hamper meaningful conclusions for clinicians.

INTRODUCTION

Prostate cancer (PCa) is one of the most frequent cancers in men, with about 6600 new cases diagnosed per year.[1] Despite its increasing incidence, a global mortality decline has been observed, in most world regions.[2] The detection of low-stage cancers (≤T2), with a better prognosis, related to the increasing incidence of the tumour and proactive screening, may contribute towards a decline in the overall mortality trend, along with improvements in PCa treatment, which is unrelated to the number of cases diagnosed.[2]

Low-stage cancer includes PCa confined to the prostate gland. Local advanced disease includes extraprostatic extension, which is defined as cancer located outside the confines of the prostate, often mixed with adipose tissue. It may also include seminal vesicle involvement. It is very useful to differentiate T2 (organ confined PCa) from T3 (local advanced disease) in order to differentiate patients who may benefit from radical surgery.

Radical prostatectomy has been the gold standard for surgical treatment for organ confined PCa.[3] Robotic-assisted radical prostatectomy introduced a minimally invasive surgical treatment for PCa and has been gaining acceptance for surgeons and patients.[4]

The detection of extraprostatic extension prior to treatment, in patients with PCa, affects the cancer prognosis. Positive surgical margin is defined as cancer cells touching an inked surgical margin on the pathological specimen. Extracapsular extension (ECE) is a cause of high frequency of PMS, biochemical recurrence, metastatic disease and lower cancer-specific survival after radical prostatectomy.[4–8]

So far, to predict the risk of advanced disease, clinicians often use staging nomograms. These nomograms, as D'AMICO or CAPRA, are based on prostate specific antigen results in blood test, biopsy Gleason score and clinical T stage on digital rectal examination; additionally, patient's age and percentage of positive biopsy cores are also included in European patients for CAPRA classification.[9 10]

Several studies demonstrated an improved accuracy in predicting ECE (pECE), by incorporating information from MRI. The combined use of MRI and clinical risk further improves prediction of pathologic ECE.[11]

MR scanners able of acquiring high spatial resolution imaging, along with functional sequences (perfusion, DWI), paved the way to the so-called multiparametric MRI (mpMRI) that has radically changed the non-invasive perception for primary diagnosis and staging of prostate carcinoma.[12] MpMRI is a well-established imaging modality in PCa assessment, particularly for depicting clinically significant PCa and improves the yields of transrectal US-guided biopsy.[13–16] MpMRI is also an accurate method for local staging of PCa, as proven by a recent meta-analysis, but with a heterogeneous sensitivity across the several studies.[17]

Current mpMRI criteria, used to detect and pECE on pathology analysis, pathologic lymph nodes status and local or biochemical recurrence (BCR), are mostly qualitative with high reader variability, owing to strong interpreter dependency and experience.[17] These include capsular contact length, capsular irregularity and/or bulging, obliteration of rectoprostatic angle, asymmetry of the neurovascular bundles, invasion of the periprostatic fat and seminal vesicle invasion.[18] Some studies that applied confidence levels to diagnose ECE, such as a Likert scale from 1 to 5, showed only a moderate inter-reader agreement, but no imaging MRI scale for PCa local staging has been proposed or accepted, so far.[19] Additionally, a few studies that have used specific Prostate Imaging Reporting and Data System findings as criteria for the assessment of pECE, revealed only a moderate overall accuracy (63%).[20 21] There is, still, a great deal of heterogeneity in the protocols and methods used in the various published studies. This variability is one of the reasons why mpMRI is not yet accepted as the standard technique for local staging, both by the European Association of Urology and the National Comprehensive Cancer Network Guidelines.[22] The only exception is, since 2016, the acceptance of mpMRI for assessing clinical tumour stage in high-risk patients.[23]

On the other hand, pECE is dependent on the mechanical effects introduced by the histological processing of the specimen, which may create additional bias and discrepancy regarding in vivo mpMRI observations. By the time, the classical MRI reported features, mentioned before, are not specific, but only suspicious for microscopic ECE. It is crucial to introduce predictive models for 'early ECE' before prostatectomy.

Artificial intelligence (AI) or machine learning (ML) is inspired by artificial neural networks (ANN), which in turn are biologically inspired algorithms. The term network is named after the topology, since neural networks represent the synergistic effect of composing and associate many different layers of information together to derive the final output. AI will lead to significant changes for radiology and how radiologists will practice.[24] ANN have been applied to the detection of PCa by several groups and successfully applied to determine the probability of malignancy using data obtained by mpMRI.[25]

Radiomics is a recent methodology that has the goal of extracting a large amount of diagnostic features (kurtosis, skewness, wavelets, etc) from specific regions in medical images through data-characterisation algorithms, in order to classify a specific physiological target.[26] These features can be used to provide valuable information to the clinician and may assist on the choice of personalised therapies. This novel method combines ideas from different scientific disciplines, transforming medical images into minable data in the form of features, exploiting that data to train ML models, so they can provide equivalent or even more accurate performance to tackle common diagnostic problems.[26 27] Radiomics have been recruited to detect, characterise but also predict clinical outcomes in various diseases, including PCa.[26] These algorithms need significantly high number of patients for training the models and hold out test sets to validate them. Due to the small patient sample for the AI standards, various dimensionality reduction methods will be used to minimise overfitting, including ensemble and transfer learning. The final Radiomic signatures will be compared in terms of performance with standard clinical nomograms and in addition novel nomograms including radiomic features will be developed.[28] As far as we know, clinically accepted and validated algorithms to pECE, obtained from mpMRI features have not been described.

OBJECTIVES

The aim of this systematic review is to analyse the AI and Radiomics models for detecting ECE and helping the surgeon to be potentially more proficient in terms of surgical outcome. Concurrently, it is also important to analyse if the models using advanced tumour segmentation and ML capabilities could improve accuracy to detect ECE in patients that underwent prostatectomy.

METHODS AND ANALYSIS

The protocol and completed review will be reported following the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols and the PRISMA, respectively.

Eligibility criteria

Studies will be included in this review if they include:

- Adult men patients (>18 years of age), with PCa with a Gleason score>6 on presurgical prostate biopsy, and submitted to MRI before they were operated by radical prostatectomy with pathologic examination.
- MRI Human studies done in MRI scanner with 1,5Tor 3T (Tesla) equipment.

Studies with patients who underwent hormonal or radiotherapy treatment before surgery or with patients undergoing hormonal, focal therapy or radiotherapy treatment to treat PCa, are excluded.

Human studies done on scanners with less than 1,5T equipment are also excluded. We include all studies using AI algorithms, including ML algorithms based on MRI images to pECE on pathology.

The main outcome of this systematic review is the pathology detected ECE in patients with PCa who underwent radical prostatectomy. The objective is the detection of MRI imaging variables that could pECE, before surgery.

Study design

Eligible studies will be prospective cohort studies or randomised controlled trials (RCTs) with prognostic factor analysis, published in peer-reviewed journals. All the studies will only be included if information regarding PCa MRI staging and pathological PCa staging is available in the published report. The studies will have to identify MRI criteria and AI models to detect index lesion, ECE and patient's outcome who underwent prostatectomy. Cross-sectional studies, case series, case reports, case–control studies, systematic reviews, conference proceedings and Masters or PhD theses will be excluded.

Information sources and search strategy

Searches will be conducted in six electronic databases: PubMed, CINAHL (via EBSCO), EMBASE (via Elsevier), CENTRAL (Cochrane Central Register of Controlled Trials; via Wiley Online Library) and Web of Science (via Clarivate Analytics), and for the grey literature, OpenGrey and Grey Literature Network Service. Additionally, hand searches of the reference lists of all included studies and previously published systematic reviews of MRI staging of PCa will be performed. The search strategy will be developed in consultation with a medical librarian with expertise in systematic review searching. The search terms will be adjusted to the specificities of the different databases. Keywords or database-specific subject headings (eg, MeSH) and the Boolean operators 'OR' and 'AND' will be used to combine the search terms. The keywords included were "Prostate neoplasm", "Machine learning", "Artificial intelligence", "Radiomics", "Deep learning", "Staging" and "Magnetic Resonance Imaging" (online supplemental file).

Study selection and data extraction

No area restriction will be applied and only studies published in the English language will be included. The search in each database will be performed from January 2007 to January 2021.

Two independent reviewers will conduct the selection process. All records identified in the search stage will be screened by title/abstract and studies clearly not matching the criteria will be discarded. The remaining studies will be full-text reviewed and included or discarded according to the inclusion/exclusion criteria. Any disagreement between the reviewers will be solved by consensus or by a third one if necessary. Reasons for the exclusion of full text records will be recorded. Details on the selection process of the studies will be documented into a flow chart following the PRISMA.

Assessment of risk of bias

Risk of bias of individual studies will be assessed independently by two reviewers. Since we will be including diverse types of studies, we will use different tools to assess the risk of bias depending of the characteristics of the studies. For all studies the RCT and non-randomised studies we will be using the QUADAS-2 tool for assessing risk of bias. This tool covers seven sources of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias for RCT. For each one of the them the risk can be assessed as high risk, unclear risk or low risk depending of the information offered by the study. Non-randomised trials such as cohort studies or case control studies will be assessed based on three perspectives: (1) selection of study groups; (2) comparability of the groups; (3) ascertainment of exposure (in case–control studies) or outcome of interest (in cohort studies). Data from these studies will be extracted and tabulated, and then reviewed for risk of bias and applicability using the QUADAS-2 tool. All evaluations will be done in duplicate. Studies with a high risk of bias and low applicability will be excluded.

A narrative synthesis will be conducted, acknowledging the risk of bias and the strength and consistency of significant associations. We will extract and report all unadjusted and adjusted measures of association from included studies. Associations with outcome will be defined as a significant (p0.2) univariable association, a significant (p0.05) adjusted association (multivariable) or a significant (p0.05) association in other predictive analysis (linear or multiple regression). Effect sizes will be represented as an OR or relative risk (RR) and considered as significant when the 95% CI do not include. The results will be analysed using the levels of evidence proposed by Furlan *et al*[29]: (A) strong evidence, defined as consistent (>75%) findings among multiple (≥2) high-quality studies; (B) moderate evidence: findings in one high-quality study and consistent (>75%) findings in≥2 low-quality studies; (C) limited evidence: findings in one high-quality study or consistent findings in≥3 low-quality studies; (D) conflicting or inconclusive evidence: consistent findings in<75% of the studies, or results based on one single study.

The possibility of performing a formal meta-analysis will be evaluated, depending on the numbers, quality and outcome variables and effect measures.

Patient and public involvement

This is a protocol for a systematic review that will be based on previously published data, therefore no participant recruitment will take place. The involvement of participants on the recruitment and dissemination of results is not applicable.

ETHICS AND DISSEMINATION

This work will be based on data that is public and already published, therefore an ethical approval is not necessary. The result obtained from this work will be published in a peer-reviewed journal and disseminated in relevant conferences and thesis elaboration. If any amendments are needed due to deviations from this protocol in the execution of the study, they will be recorded and noted in the publication.

Correction notice This article has been corrected since it was published Online First. One of the authors name has been updated.

Contributors The manuscript protocol was drafted by AG and was revised by EN. NP contributed for the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. HD will develop the search strategy and manage the study records on Mendeley software. AG and EN will screen the studies obtained in the search for their eligibility criteria, extract data and assess risk of bias of included studies. NP will resolve any disagreements regarding eligibility for inclusion, data extraction and/or risk of bias. All authors have read, provided feedback and approved the final protocol. AG is the guarantor of this article.

Funding This work is supported by a PhD student scholarship supported by Luz Saúde Clinical Research and Innovation programme.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs

Adalgisa Guerra http://orcid.org/0000-0002-0095-5662
Eduardo Negrão http://orcid.org/0000-0003-3621-9699
Nickolaos Papanikolaou http://orcid.org/0000-0003-3298-2072
Helena Donato http://orcid.org/0000-0002-1905-1268

REFERENCES

1 Global Cancer Observatory [Internet]. Available: https://gco.iarc.fr/ [Accessed 16 Feb 2020].
2 Pina F, Castro C, Ferro A, *et al*. Prostate cancer incidence and mortality in Portugal: trends, projections and regional differences. *Eur J Cancer Prev* 2017;26:404–10.
3 Johnson MT, Ramsey ML, Ebel JJ, *et al*. Do robotic prostatectomy positive surgical margins occur in the same location as extraprostatic extension? *World J Urol* 2014;32:761–7.
4 Ficarra V, Novara G, Secco S, *et al*. Predictors of positive surgical margins after laparoscopic robot assisted radical prostatectomy. *J Urol* 2009;182:2682–8.
5 Hull GW, Rabbani F, Abbas F, *et al*. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol* 2002;167:528–34.
6 Mikel Hubanks J, Boorjian SA, Frank I, *et al*. The presence of extracapsular extension is associated with an increased risk of death from prostate cancer after radical prostatectomy for patients with seminal vesicle invasion and negative lymph nodes. *Urol Oncol* 2014;32:26.e1–26.e7.
7 Tollefson MK, Karnes RJ, Rangel LJ, *et al*. The impact of clinical stage on prostate cancer survival following radical prostatectomy. *J Urol* 2013;189:1707–12.
8 Wheeler TM, Dillioglugil O, Kattan MW, *et al*. Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer. *Hum Pathol* 1998;29:856–62.
9 Reisæter LAR, Fütterer JJ, Losnegård A, *et al*. Optimising preoperative risk stratification tools for prostate cancer using mpMRI. *Eur Radiol* 2018;28:1016–26.
10 D'Amico AV. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*1998;280:969.
11 Chun FK-H, Steuber T, Erbersdobler A, *et al*. Development and internal validation of a nomogram predicting the probability of prostate cancer Gleason sum upgrading between biopsy and radical prostatectomy pathology. *Eur Urol* 2006;49:820–6.
12 Hoeks CMA, Barentsz JO, Hambrock T, *et al*. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. *Radiology* 2011;261:46–66.
13 Johnson LM, Turkbey B, Figg WD, *et al*. Multiparametric MRI in prostate cancer management. *Nat Rev Clin Oncol* 2014;11:346–53.
14 Ahmed HU, Arya M, Freeman A, *et al*. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? *Lancet Oncol* 2012;13:e509–17.
15 Kasivisvanathan V, Rannikko AS, Borghi M, *et al*. MRI-Targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med Overseas Ed* 2018;378:1767–77.
16 Verma S, Choyke PL, Eberhardt SC, *et al*. The current state of Mr Imaging–targeted biopsy techniques for detection of prostate cancer. *Radiology* 2017;285:343–56.
17 de Rooij M, Hamoen EHJ, Witjes JA, *et al*. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. *Eur Urol* 2016;70:233–45.
18 Kongnyuy M, Sidana A, George AK, *et al*. Tumor contact with prostate capsule on magnetic resonance imaging: a potential biomarker for staging and prognosis. *Urol Oncol* 2017;35:30.e1–30.e8.
19 Costa DN, Passoni NM, Leyendecker JR, *et al*. Diagnostic utility of a Likert scale versus qualitative descriptors and length of capsular contact for determining extraprostatic tumor extension at multiparametric prostate MRI. *AJR Am J Roentgenol* 2018;210:1066–72.
20 Kayat Bittencourt L, Litjens G, Hulsbergen-van de Kaa CA, *et al*. Prostate cancer: the European Society of urogenital radiology prostate imaging reporting and data system criteria for predicting Extraprostatic extension by using 3-T multiparametric MR imaging. *Radiology* 2015;276:479–89.
21 Schieda N, Quon JS, Lim C, *et al*. Evaluation of the European Society of urogenital radiology (ESUR) PI-RADS scoring system for assessment of extra-prostatic extension in prostatic carcinoma. *Eur J Radiol* 2015;84:1843–8.
22 Mohler JL, Armstrong AJ, Bahnson RR, *et al*. Prostate cancer, version 1.2016. *J Natl Compr Canc Netw* 2016;14:19–30.
23 Mottet N, Bellmunt J, Bolla M, *et al*. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618–29.

24 Recht M, Bryan RN. Artificial Intelligence: Threat or Boon to Radiologists? *J Am Coll Radiol* 2017;14:1476–80.
25 Cosma G, Brown D, Archer M, *et al*. A survey on computational intelligence approaches for predictive modeling in prostate cancer. *Expert Syst Appl* 2017;70:1–19.
26 Stoyanova R, Takhar M, Tschudi Y, *et al*. Prostate cancer radiomics and the promise of radiogenomics. *Transl Cancer Res* 2016;5:432–47.
27 Toivonen J, Montoya Perez I, Movahedi P, *et al*. Radiomics and machine learning of multisequence multiparametric prostate MRI: towards improved non-invasive prostate cancer characterization. *PLoS One* 2019;14:e0217702–23.
28 Schwier M, van Griethuysen J, Vangel MG, *et al*. Repeatability of multiparametric prostate MRI Radiomics features. *Sci Rep* 2019;9:9441.
29 Furlan AD, Malmivaara A, Chou R, *et al*. 2015 updated method guideline for systematic reviews in the Cochrane back and neck group. *Spine* 2015;40:1660–73.