Observational Study
Lutetium in prostate cancer: Reconstruction of patient-level data from published trials and generation of a multi-trial Kaplan-Meier curve

Andrea Messori

**Abstract**

**BACKGROUND**
Lutetium has been shown to be an important potential innovation in pre-treated metastatic castration-resistant prostate cancer. Two clinical trials have evaluated lutetium thus far (therap and vision with 99 and 385 patients, respectively), but their results are discordant.

**AIM**
To synthetize the available evidence on the effectiveness of lutetium in pre-treated metastatic castration-resistant prostate cancer; and to test the application of a new artificial intelligence technique that synthetizes effectiveness based on reconstructed patient-level data.

**METHODS**
We employed a new artificial intelligence method (shiny method) to pool the survival data of these two trials and evaluate to what extent the lutetium cohorts differed from one another. The shiny technique employs an original reconstruction of individual patient data from the Kaplan-Meier curves. The progression-free survival graphs of the two lutetium cohorts were analyzed and compared.

**RESULTS**
The hazard ratio estimated was in favor of the vision trial; the difference was statistically significant ($P < 0.001$). These results indicate that further studies on lutetium are needed because the survival data of the two trials published thus far are conflicting.

**CONCLUSION**
Our study confirms the feasibility of reconstructing patient-level data from
survival graphs in order to generate a survival statistics.

Key Words: Survival analysis; Individual patient data reconstruction; Kaplan-Meier curves; Meta-analysis; Prostate Cancer; Lutetium

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This paper describes the application of a new technique of individual-patient data reconstruction to the progression-free survival curves published in two trials evaluating lutetium in metastatic prostate cancer. Our analysis interpreted these survival data and showed discordant results between the two trials, that need to be addressed by further clinical research.

INTRODUCTION

Lutetium has been shown to be an important potential innovation in pre-treated metastatic prostate cancer, but the extent to which outcomes are improved by this treatment still needs to be fully investigated. Three studies have evaluated lutetium in this disease condition. One was phase II (therap trial[1]), the second was phase III (vision trial[2]); the third, which was an observational real-world study[3], differed from the first two because lutetium was given after radium-223.

In recent times, techniques that reconstruct individual patient data from the graphs of Kaplan-Meier curves have considerably improved in terms of performance and easy applicability[4]. One advantage is that the availability of these techniques permits to combine multiple survival curves published in different trials without using any meta-analytical statistics. An example of this approach is presented herein. Our objective was two-fold: 1) to quantify the gain in progression-free survival determined by lutetium; 2) to demonstrate the applicability of techniques of patient-level data reconstruction in addressing specific questions based on time-to-event endpoints without the need to employ any meta-analytic statistics.

MATERIALS AND METHODS

We applied the shiny technique of individual patient data reconstruction[4] to the Kaplan-Meier graphs of progression-free survival reported in the therap phase-II trial[1] and in the vision phase III trial[2]. Both trials were conducted in patients with metastatic castration-resistant prostate cancer previously treated for their metastatic disease. In the therap trial, the treatment group received Lu-PSMA-617 (6.0–8.5 GBq intravenously every 6 wk for up to six cycles) while the controls were given cabazitaxel (20 mg/m² intravenously every 3 wk for up to ten cycles). In the vision trial, the treatment group received 177Lu-PSMA-617 (7.4 GBq every 6 wk for four to six cycles) plus protocol-permitted standard care while the controls received standard care alone. In the therap trial, progression-free survival was defined as the interval from randomisation to first evidence of pupil-size artefact progression defined by an increase of at least 25% and at least 2 ng/mL after 12 wk (as per PCWG316), radiographic progression using locally reported computed tomography and bone scanning [Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and PCWG3 criteria for bone lesions], commencement of non-protocol anticancer treatment, or death from any cause. In the vision trial, the end-point was image based progression free survival.

The progression-free survival graphs of the two lutetium cohorts by Hofman et al[1] for the therap trial (99 patients; follow-up of 18 mo; 90 events) and Sartor et al[2] for the vision trial (385 patients; follow-up of 30 mo; 254 events). For each of these two Kaplan-Meier curves, the graph was digitalized and converted into x-y data pairs using Webplotdigitizer (version 4.5, https://apps.automeris.io/wpd/). Then, the shiny package (version: 1.2.2; subprogram “Reconstruct Individual Patient Data”; https://www.trialdesign.org/one-page-shell.html#IPDfromKM, see reference [4]) was used to reconstruct patient-level data on the basis of x-y data pairs, total number of enrolled patients, and total number of events. Finally, the pooled survival curves were generated from the reconstructed patient-level data and analyzed through standard Cox statistics. For this purpose we used
三 packages (”coxph”, “survfit”, and “ggsurvplot”) under the R-platform. The hazard ratio (HR) was estimated.

RESULTS

The shiny procedure combined with standard Kaplan-Meier statistics allowed us to compare the 99 patients given lutetium in the therap trial with the 385 patients given lutetium in the vision trial. Figure 1 shows the two Kaplan-Meier curves generated from reconstructed patient-level data. The HR estimated from these curves favored the patients of the vision trial and was 0.59 (95%CI, 0.46 to 0.75). The difference was statistically significant (P < 0.001).

DISCUSSION

When two or more randomised trials are available on a therapeutic issue and the clinical end-point is the form of time-to-event, synthesising the clinical evidence is a complex issue, and there is presently no consensus on which methodological approach should be preferred.[5,6] Pooling the values of HR is certainly the method most commonly used, but its important limitations have been widely recognised for many years (e.g. the inability to account for the length of follow-up, the inability to model variations of risk over time, the dimensionless nature of HR as opposed to the greater informative value of absolute parameters such as medians, etc.)[8]. The development of the restricted mean survival time has represented an advancement in this field[8,9], but the use of this parameter unfortunately remains low.

In this context, the marked improvement in performance of techniques that reconstruct individual-patient data[4] represents an important innovation, the role of which still needs to be fully evaluated. On the one hand, reconstructing individual-patient data is a mandatory pre-requisite to determine the RMST, and this explains the increased use of these reconstruction techniques when a single trial needs to be analysed[7]. On the other hand, another potential use of these techniques is being recognised when multiple trials are available: in such cases, these techniques offer a new methodological alternative to standard meta-analytic methods[5,6] and also to the more recent approaches where meta-analysis is based on the use of RMSTs[8,9].

The various parameters mentioned above (especially HR, RMST, and median) have been investigated for many years to identify their respective advantages and disadvantages, and the literature on this issue is wide[7]. In contrast, the literature on the use of reconstructed survival curves is still in its early stages[4,6], and this holds true particularly when multiple trials are analysed and pooled together.

The experience described herein offers a limited but useful contribution to the development of meta-analysis-like methods based on reconstructed survival curves. The two control groups of the two trials differed in the treatment they received, and so were not included in our analysis, which was focused only on the two lutetium groups of the two trials. In comparing these two group with one another, our results raise the need to explain the statistically different outcomes shown by the HR and presented in Figure 1.

The inclusion criteria of the therap and vision trials were very similar, and so they likely had no substantial role in determining this difference. In fact, in the therap trial, patients had metastatic castration-resistant cancer and PET eligibility criteria for the trial were PSMA-positive disease, and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings; previous treatment with androgen receptor-directed therapy was allowed. In the vision trial, patients had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens and had PSMA-positive gallium-68 (68Ga)-labeled PSMA-11 and PET scans. While these differences in the inclusion criteria do not seem to suggest a better prognosis for patients included in either trial, a number of factors (e.g. environmental and lifestyle factors, tissue biomarkers, molecular pathological epidemiology, the microbiota, etc.) might have influenced tumor development and response to therapy. Hence, the discrepancies observed across the two trials included in our analysis might be explained by these factors. As regards innovative treatments such as lutetium, it should be stressed that molecular pathological epidemiology research has a growing role and is increasingly recognized to be a promising strategy to improve prediction of response to therapy.

In summary, the main strength of our analysis lies in the originality of the methodological approach that reflects the recent availability of very efficient patient data reconstruction techniques. The main limitation is represented by the indirect nature of the comparison between the two lutetium cohorts.

CONCLUSION

Our study indicates that further studies on Lu-PSMA-617 are needed because the survival data of the
two trials published thus far demonstrate quite conflicting results. The example described in this paper confirms the feasibility of reconstructing patient-level data from survival graphs in order to generate a survival statistics from these reconstructed data. To evaluate the advantages and disadvantages of this new methodological approach, further analyses will be needed.

**ARTICLE HIGHLIGHTS**

**Research background**
Two trials have been published to assess the effectiveness of lutetium in metastatic prostate cancer. The need to convert these effectiveness data into a pooled estimate represents a useful opportunity to test an innovative technique of individual patient reconstruction based on the analysis of Kaplan-Meier curves (shiny method).

**Research motivation**
The main motivation was to test the performance of the shiny method based on a real data-set.

**Research objectives**
Clarifying the effectiveness of lutetium in metastatic prostate cancer and confirm the reliability of the shiny method as a tool for reconstructing individual patient data.

**Research methods**
The clinical trials that have thus far evaluated lutetium in metastatic prostate cancer have been identified by standard literature search. A pooled survival curve has been generated from these trials by using the shiny technique of individual patient data reconstruction.
Research results
Two clinical trials were identified. A pooled Kaplan-Meier survival curve was generated that synthesizes the current evidence on the effectiveness of this treatment in this disease condition.

Research conclusions
A two-fold conclusion: first, lutetium is effective in metastatic prostate cancer; second, the Shiny technique can successfully be used to pool survival data from two trials without employing any meta-analytical method.

Research perspectives
The shiny technique has been confirmed to be a useful new tool for analyzing survival data from multiple trials and therefore deserves to be further applied in the analysis of clinical evidence.

FOOTNOTES
Author contributions: Messori A is the sole author, read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Italy

ORCID number: Andrea Messori 0000-0002-5829-107X.

Corresponding Author’s Membership in Professional Societies: Sifact

REFERENCES
8 Messori A, Bartoli L, Trippoli S. The restricted mean survival time as a replacement for the hazard ratio and the number needed to treat in long-term studies. ESC Heart Fail 2021; 8: 2345-2348 [PMID: 33733263 DOI: 10.1002/ehf2.13306]
Dear Dr. Messori,

We are pleased to inform you that your paper has successfully passed our very rigorous review process and has been accepted for publication in the *World Journal of Methodology*.

1 BASIC INFORMATION OF THE MANUSCRIPT

**Manuscript NO:** 72756

**Manuscript Type:** Observational Study

**Title:** Lutetium in prostate cancer: Reconstruction of patient-level data from published trials and generation of a multi-trial Kaplan-Meier curve

**Authors:** Andrea Messori

**Corresponding author:** Andrea Messori, PharmD, Senior Researcher, HTA, ESTAR Toscana and Regione Toscana, via Alderotti 26/N, Firenze 50139, Italia, Italy. andrea.messori.it@gmail.com

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Copyright:** © The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

**Received Date:** 2021-10-26

**Accepted Date:** 2022-03-17

**In Press:** https://www.f6publishing.com/ArticleInPressDetail?id=72756

**Publication Fee:** 898.00 USD

**Discounted Publication Fee:** 808.00 USD
**READERSHIP:** The purpose of accurately sending your Original Article to highly influential 1000-10000 experts is to enable more peers to read, share, and cite your published research results, to help enhance your global academic influence, and to promote the overall development of the field. After completing this, we will formally notify you of the number of experts to whom your manuscript is sent via email.

**2 HOW TO MAKE THE PAYMENT**

**Step 1:** If you need the signed acceptance letter (Word document), please click [Acceptance Letter](#) to download it.

**Step 2:** Please click [Invoice](#) to download the invoice for the Publication Fee and Reprints Fee.

**Step 3:** Please make the payment within **7 days** after receiving this notification letter, according to the following instructions.

Please indicate the Manuscript NO. of your article (72756) in the payment description field on the application form to facilitate processing of your article.

The forms of payment accepted are:

**Bank Transfer**

**Account Name:** BAISHIDENG PUBLISHING GROUP INC

**Account Number:** 164101946543

**Receiving Bank Name:** Bank of America

**Swift Code:** BOFAUS3N

**ABA/Routing Number:** 026009593

**Receiving Bank Address:** 337 Main St, Pleasanton, CA 94566, USA

**Credit card**

For your convenience, we have included a "pay now" link to our website which allows you to pay this invoice directly via credit card. Click [here](#) or copy and paste this address into your browser: [https://www.wjgnet.com/bpg/payinvoice](https://www.wjgnet.com/bpg/payinvoice)

**Check**
Not accepted.

**Step 4:** After you complete the payment, please login to the F6Publishing system ([https://www.f6publishing.com](https://www.f6publishing.com)) and click on the “Accepted Manuscripts with Publication Fee Required” to submit the following information: Publication Fee, Reprints Fee, and Currency. Finally, please upload the Remittance Voucher (PDF or JPG).

Upon receipt of the total publication fee, we will begin the publication process for your article. Once your article is published, we will forward a high-resolution electronic version of your article to you.

In order to publish your article promptly, we strongly recommend that you carry out your actions with consideration to our publication fee policies: (1) Generally, publication fees will not be waived or discounted in any way; and (2) A publication fee will not be refunded if the authors withdraw their article during the publication process.

### 3 COMPANY EDITOR-IN-CHIEF’S COMMENTS

All documents of the manuscript have met the publication requirements of the World Journal of Methodology, and the manuscript is given final acceptance for publication. We will arrange the manuscript production. As the manuscript has been finally accepted, the following rules apply without exception in this proofreading process: (1) We do not allow the manuscript title to be changed; (2) We do not allow the order of authors to be changed, the authors and corresponding authors to be changed or deleted, or for any new authors to be added; (3) We do not allow any funding agency or grant number to be added or deleted; (4) We do not allow the manuscript text to be added or deleted; (5) We do not allow any figures or tables to be added or deleted; (6) We do not allow manuscript references to be added or deleted; and (7) We do not allow any part of the manuscript to be revised after formal online publication.

Finally, on behalf of the Editors of the World Journal of Methodology, I would like to thank you for your cooperation. We look forward to your continued contributions to the journal.

If you have any questions, please feel free to contact us via e-mail at: publicationfee@wjgnet.com or online at the Help Desk: [https://www.f6publishing.com/helpdesk](https://www.f6publishing.com/helpdesk).

Best regards,

Lian-Sheng Ma, Founder and Chief Executive Officer

**Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-399-1568

**E-mail:** ls.ma@baishideng.com