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Original research

Radiomic features of primary retroperitoneal sarcomas: a prognostic study

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ABSTRACT

Background: Risk-stratification of patients with retroperitoneal sarcomas (RPS) relies on validated nomograms, such as Sarculator. This retrospective study investigated whether radiomic features extracted from computed tomography (CT) imaging could *i*) enhance the performance of Sarculator and *ii*) identify G3 dedifferentiated liposarcoma (DDLPS) or leiomyosarcoma (LMS), which are currently consider in a randomized clinical trial testing neoadjuvant chemotherapy.

Methods: Patients with primary localized RPS treated with curative-intent surgery (2011–2015) and available pre-operative CT imaging were included. Regions of interest (ROIs) were manually annotated on both unenhanced and portal venous phase acquisitions. Top performing radiomic features were selected with outcome-specific random forest models, through generation of replicative experiments (contexts) where patients were split into training and testing sets. Endpoints were overall and disease-free survival (OS, DFS).

Prognostic models for DFS and OS included the top five selected radiomic features and the Sarculator nomogram score.

Models accuracy was assessed with Harrell's Concordance (C-)index.

Results: The study included 112 patients, with a median follow-up of 77 months (IQR 65–92 months).

Sarculator alone achieved a C-index of 0.622 and 0.686 for DFS and OS, respectively. Radiomic features only marginally enhanced the prediction accuracy of Sarculator for OS (C-index=0.726, C-index gain: 0.04) or DFS (C-index=0.639, C-index gain: 0.017). Finally, radiomic features identified patients with G3 DDLPS or LMS with an accuracy of 0.806.

Conclusion: Radiomic features marginally improved the performance of Sarculator in RPS.

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However, they accurately identified G3 DDLPS or LMS at diagnosis, potentially improving patients selection for neoadjuvant treatments.

1. Introduction

Sarculator is a publicly available collection of prognostic nomograms utilized to predict overall and disease free-survival or incidence of distant metastases in patients who underwent surgical resection of primary or soft-tissue sarcomas of the extremities (ESTS) or retroperitoneal sarcomas (RPS).

Its widespread popularity partially derives from its ease of use, as it includes readily obtainable and reproducible patient- and tumour-related characteristics [1–3].

We hypothesized that the accuracy of prognostic risk stratification could potentially be enhanced by utilizing information gathered during pre-operative staging with computed tomography (CT) [4–6].

In the near future, pre-operative imaging might serve as a "virtual biopsy" and provide imaging biomarkers for further computational analysis [7].

Radiomics is an emerging quantitative approach that relies on the extraction, processing and downstream analysis of high-dimensional data derived from biomedical images, leveraging the underlying hypothesis that they retain meaningful biological information. [8–11].

The radiomic workflow is a multistep process entailing image preprocessing, lesion segmentation, feature extraction and selection, model development and validation. To date, radiomics has been mainly challenged to perform either classification (e.g., discriminating benign vs. malignant lesions) or prediction tasks (stratification of patients based on the likelihood of occurrence of defined clinical endpoints).

A recent study demonstrated that radiomic features accurately predict histology and malignancy grade in dedifferentiated liposarcomas (DDLPS) and leyomiosarcomas (LMS) [12].

Our study aimed at: *i*) evaluating the prognostic value of radiomic features in predicting overall survival (OS) and disease-free survival (DFS) for patients with primary localized RPS treated with surgery, particularly when combined with the Sarculator nomograms; and *ii*) confirm the predictive accuracy of radiomic features in identifying G3 retroperitoneal DDLPS or LMS, which constitute the target population for a phase III RCT comparing neoadjuvant anthracycline-based chemotherapy followed by surgery versus surgery alone [13,14]. To increase findings reproducibility, analyses exploited radiomic features from non-contrast enhanced CT scan and explorative analysis were conducted to investigate considering also radiomic features from non-contrast enhanced CT scan.

2. Methods

2.1. Patients

This retrospective study included patients with primary localized RPS treated with surgery. Detailed information about study selection criteria are reported as Supplementary material.

This study was approved by the Ethics Committee of INT (ID: 77/18) as part of a broader institutional research project entitled "Integration of radiomics, genomics, and immunoprofiling into predictive and prognostic models in soft tissue sarcoma patients (SARCOMICS study)", which aims at performing a multiomic profile of patients with extremity and retroperitoneal sarcoma.

2.2. Processing of radiomic features

Imaging acquisition parameters have already been detailed elsewhere [5].

Two radiologists with dedicate training and expertise in soft tissue sarcomas retrospectively reviewed all images. Regions of Interest (ROIs) were manually annotated slice by slice, resulting in a 3D ROI from which radiomic features were extracted.

Radiomic features pertaining to the following three main classes were extracted for each image: i) shape-and-size; ii) Intensity-based; and iii) texture. See also Supplementary material.

2.3. Statistical analysis

The present analysis was aimed at selecting the radiomic features able to predict the following outcomes: *i*) 5-year OS; *ii*) 5-year DFS; and *iii*) identify RPS belonging to specific histologic types: LMS or G3 DDLPS.

Our analysis involved the extraction of radiomic features from non-contrast-enhanced CT scans acquired before surgery and their integration with Sarculator (Fig. 1), that encompassed the following phases:

1. Phase 1 – Random split: the dataset was initially partitioned into a training set and a testing set;
2. Phase 2 – Random forest (RF) hyperparameter tuning: hyper parameters were fine-tuned;
3. Phase 3 – RF-based feature selection: utilizing a RF model, we conducted variable selection to create replicative experiments, known as 'contexts';
4. Phase 4 – Prediction forest with selected features;
5. Phase 5 - Radiomic Feature Identification: Utilizing the selected radiomic features to evaluate the accuracy of RF models in the testing set.

Detailed description of statistical methods is reported as online available Supplementary Material.

3. Results

A total of 195 patients with a primary localized RPS were treated with curative-intent surgery in the study period. Among them, radiomic features could be extracted from 116 patients who were thus deemed eligible for the study.

In 112 patients with all information required to employ Sarculator nomogram score (NS) (Supplementary Table S1), median follow-up was 77 months (IQR, 65–92 months).

Median DFS and OS were 50 months and not reached, respectively (Fig. 2A-B).

3.1. Sarculator predicted DFS and OS in the whole series

First, we assessed the distribution of the Sarculator NS in this patient series (Fig. 2C-D).

The median Sarculator NS for DFS and OS was 133 (range, 10–190; Fig. 2C) and 139 (range, 113–157); Fig. 2D) which correspond to a median 5-year DFS and 5-year OS of 0.44 (IQR 0.21–0·64) and 0.66 (IQR, 0.48–0.84), respectively. Sarculator nomogram calibration for 5-year DFS and OS demonstrated the concordance between the predicted and observed Kaplan-Meier estimates in the calibration plots. Sarculator achieved a C-index and ingenuity pathway analysis (IPA) for predicting OS of 0.686 and 0.158, and for predicting DFS 0.622 and 0.133, respectively.

3.2. Radiomic features marginally improved the performance of Sarculator

3.2.1. Disease-free survival (DFS)

To evaluate the added value of the radiomic features selected with the random forest to the performance of Sarculator, we compared the IPA and C-index obtained in a RFS model including the features selected in each context (Fig.3A) with those of Cox models including only the Sarculator NS. In 336 out of 1154 contexts (29.1 %), the IPA of the RSF was higher than the IPA of the Cox model including only the Sarculator NS.

The same comparison in terms of C-index yielded a better result in 405 of 1154 contexts (35.1 %).

The number of contexts where the RFS performed better than the Cox model including the Sarculator NS according to both IPA and C-index were 257/1154 (22.3 %).

Based on the power calculations shown in the Supplementary material, six top variables (Fig. 3B) had to be included in the final prediction model; after the Sarculator NS, the five most selected radiomic features were: *original_GLCM_MCC*, *waveletHLH_glcm_ClusterShade*, *original_shape_Elongation*, *waveletHHL_firstorder_Mean* and *waveletHLH_firstorder_Kurtosis* (Supplementary Table S2).

The *original_GLCM_MCC*, a measure of complexity of the radiomic texture, was the most selected radiomic feature (827 contexts, 71.7 %). The predictive accuracy of radiomic features without the Sarculator NS was low (c-index = 0.559; IPA = 0.016).

Lastly, we explored the gain in prognostic accuracy after adding the top 5 radiomic features to the Sarculator NS (total number of variables, N = 6) in a multivariable Cox model, which reached a C-index of 0.639, with a final gain of 0.017, and an IPA of 0.134, with a final gain of 0.001.

Although the improvement in prognostic accuracy was limited, the model maintained a good calibration (Figure 3C-D).

3.2.2. Overall survival (OS)

To evaluate the added value of the radiomic features in enhancing the Sarculator NS accuracy as described in the Supplementary material, we compared the IPA and C-index of each contest (Figure 4A) with those of the Sarculator NS calculated with the Cox model to evaluate the added value of each context.

Compared to the analysis for DFS, we identified less contexts characterized by improvements of these metrics. Specifically, the number of contexts where the IPA of the RSF was higher than the IPA of the Cox model including only the Sarculator NS was 67/1038 (6·5 %). The same comparison in terms of C-index yielded a better result in 97 of 1038 contexts (8.5 %). The number of contexts where the RSF performs better than the Cox model including nomogram score with both IPA and C-index were only 33/1038 (2.9 %).

Based on power calculation (Supplementary material), six top variables (Fig. 4B) had to be included in the final prediction model. After the Sarculator NS, the following five radiomic features were the most selected: *original_shape_Elongation, waveletHHH_firstorder_Median, original_shape_Flatness, waveletHHH_firstorder_Entropy* and *waveletHLH_glcm_ClusterShade* (Supplementary Table S2).

The predictive accuracy of radiomic features without the Sarculator NS was low (C-index = 0.581; IPA = 0.022). The Sarculator NS together with these features analysed with a multivariable Cox-model in this series reached a C-index of 0.726, with a final gain of 0.04, and an IPA of 0.188, with a final gain of 0.03.

The model had a good calibration (Fig. 4C-D).

3.3. Radiomic features identified accurately patients with G3 DDLPS or LMS

We tested the predictive accuracy of radiomic features to identify patients with G3 DDLPS or LMS.

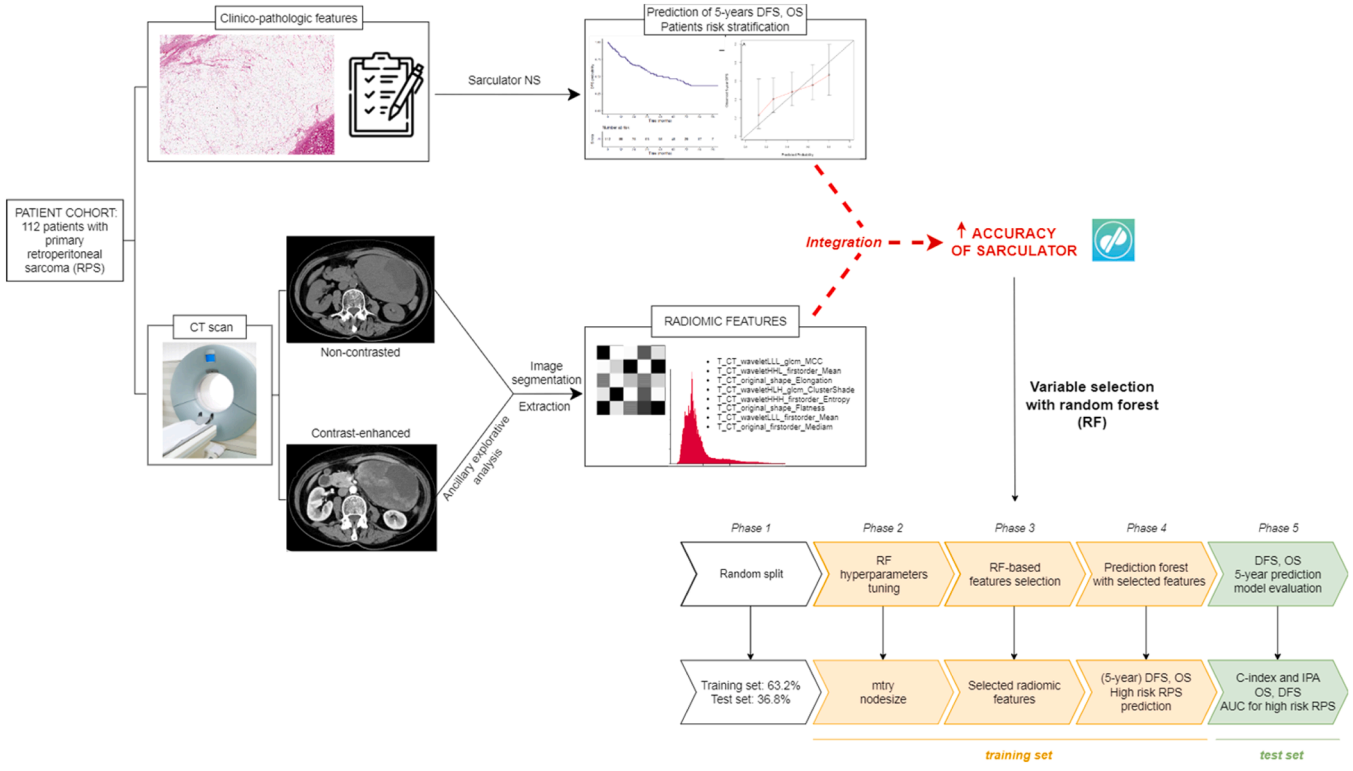

Fig. 1. Work-flow of analysis performed to extract and select radiomic features. Our analysis involved a structured pipeline where radiomic features were extracted from preoperative non-contrast-enhanced CT scans and integrated with the prediction of Sarculator. The process proceeded through various phases: i) the dataset was initially divided into a training set and a testing set (Phase 1); ii) we fine-tuned hyperparameters of random forest (Phase 2); 3) Using a random forest model, we performed variable selection to generate replicative experiments (contexts) (Phase 3); and identified radiomic features for testing in the training (Phase 4) and validation sets (Phase 5).

Based on power calculations shown in the Supplementary material, the top five radiomic features to be included in the final prediction model for the diagnosis of a G3 DDLPS or LMS (which was defined here as a positive result) were the following: *original_firstorder_10Percentile*, *waveletLLL_firstorder_10Percentile*, *waveletLLL_firstorder_Median*, *waveletLLL_firstorder_90Percentile* and *original_firstorder_Median* (Figure 5A).

In the binary logistic model that included the 5 selected features, predictive probabilities were derived and represented in the calibration plot, showing a good calibration (Fig. 5B).

The ROC curve derived from this model is shown in Fig. 5C and had an AUC of 0.806.

To minimize the event of a high-risk RPS patient being wrongly classified (negative result), we identified in the ROC curve the cut-point of 0.229 (red line in Fig. 5D), which resulted in 4 false negative (FN) patients (3.5 %; red dots in Fig. 5D) with a sensitivity of 90 % and a negative predictive value (NPV) of 91.1 %.

Additionally, we tried to identify a cut-off to minimize the misclassification of patients as G3 DDLPS or LMS [false positive (FP) result]. A cut-point of 0.5609 applied on the predictive probabilities (horizontal red line in Fig. 5E) resulted in 11 FP patients (9.5 %; red dots), a specificity of 85.5 % and a positive predictive value (PPV) as low as 64.5 %.

3.4. Explorative analysis with radiomic features from contrast-enhanced CT scans

Ancillary analyses evaluated the potential added value of radiomic features extracted from contrast-enhanced CT scans. The integration of these features increased the number of non-informative contexts when compared to analyses employing only features from unenhanced CT scans alone, possibly reflecting the increased variability of radiomic features from contrast-enhanced images. These analyses are reported in the Supplementary material.

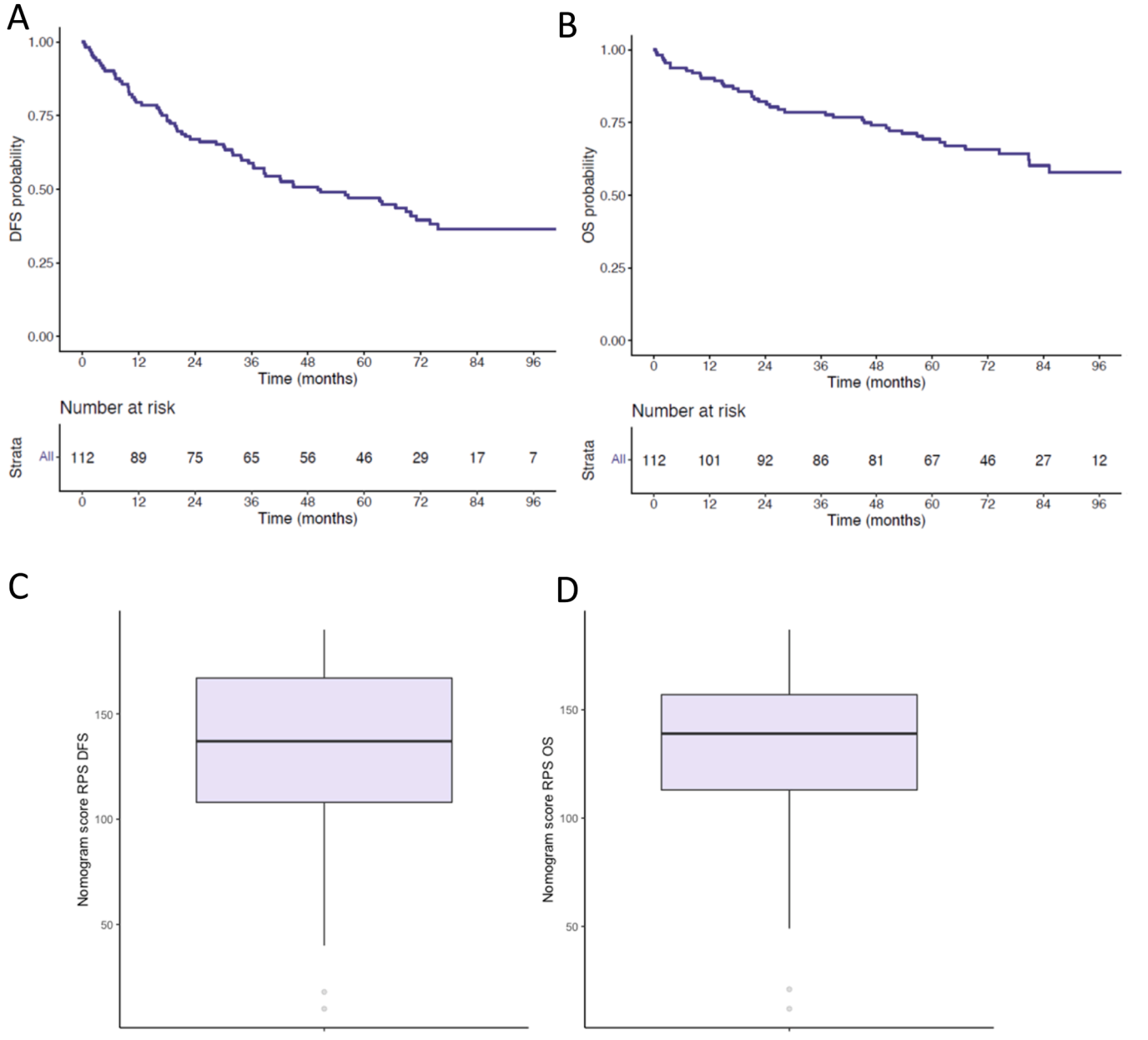

Fig. 2. Performance of the Sarculator nomogram. Panels **A** and **B**: DFS and OS Kaplan Meier curves of 112 patients with retroperitoneal sarcoma. Panels **C** and **D**: box plots representing the Sarculator score for DFS and OS.

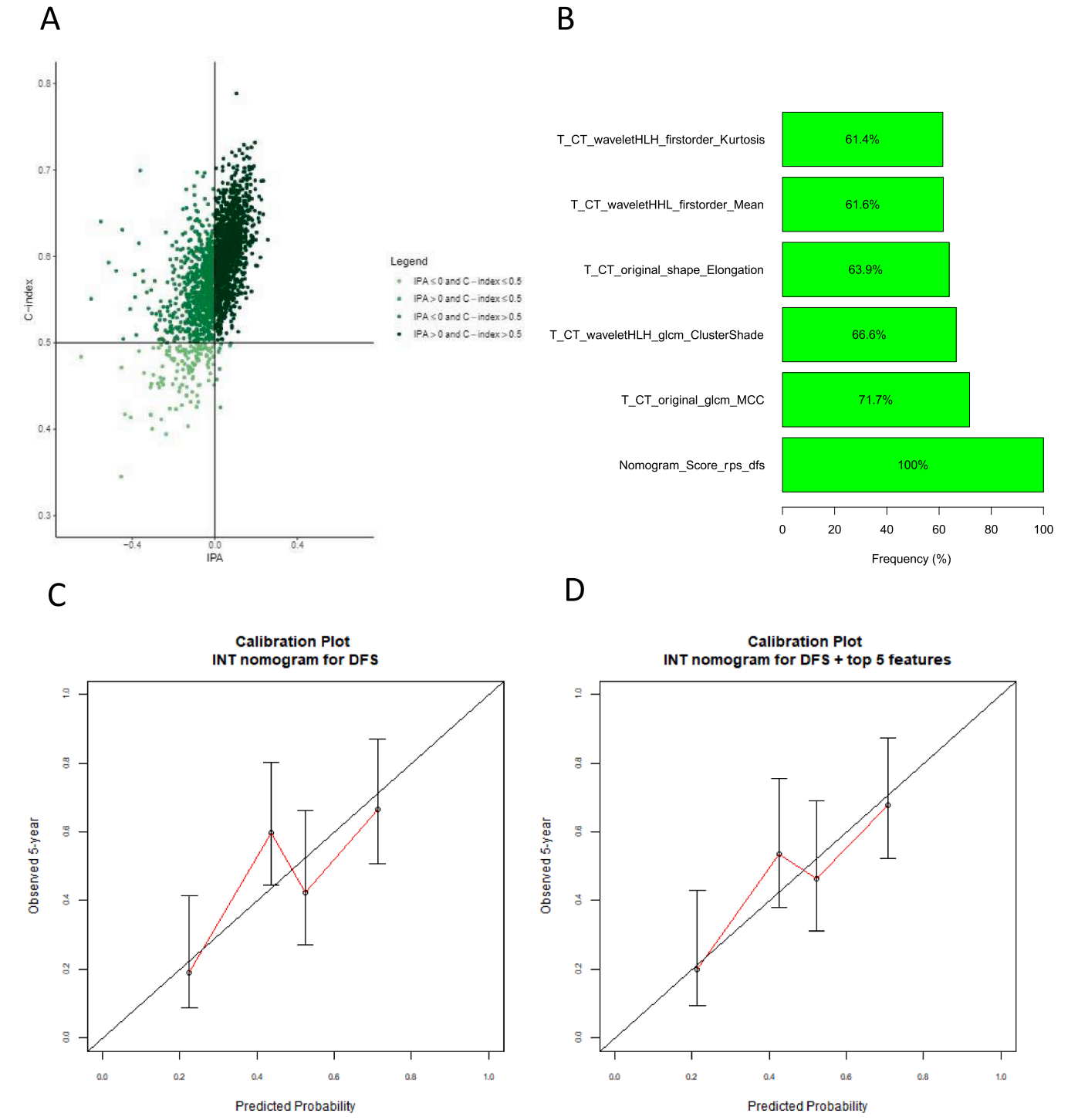

Fig. 3. Results of the random forest-based feature selection for disease-free survival and calibration of models including the selected features. Panel **A:** scatter plot of IPA (x-axis) and c-index values (y-axis) for each context. Based on these two metrics, contexts were classified as 'non-harmful' (upper right quadrant) and 'harmful' (upper left, lower left, and lower right quadrant). Panel **B:** bar plot showing the proportion of contexts in which the Sarculator and the top five radiomic features were selected. Panel **C:** calibration plot from a Cox model including the Sarculator alone. Panel **D:** calibration plot from a Cox model including the Sarculator and the top five selected radiomic features.

4. Discussion

In this retrospective study, the incorporation of radiomic features extracted from non-contrast-enhanced preoperative CT scans marginally enhanced the performance of the Sarculator NS in predicting the prognosis of patients with primary localized RPS treated with surgery [1,2,15].

Of note, radiomic features allowed to identify patients with G3 DDLPS or LMS at diagnosis.

The main limitations of this study are represented by its retrospective design and the lack of an independent validation cohort. However, these flaws have been tackled via: *i*) the generation of multiple contexts to identify non-informative or non-harmful contexts and variables; *ii*) fitting both the random forest and the Cox models with data; and *iii*) an

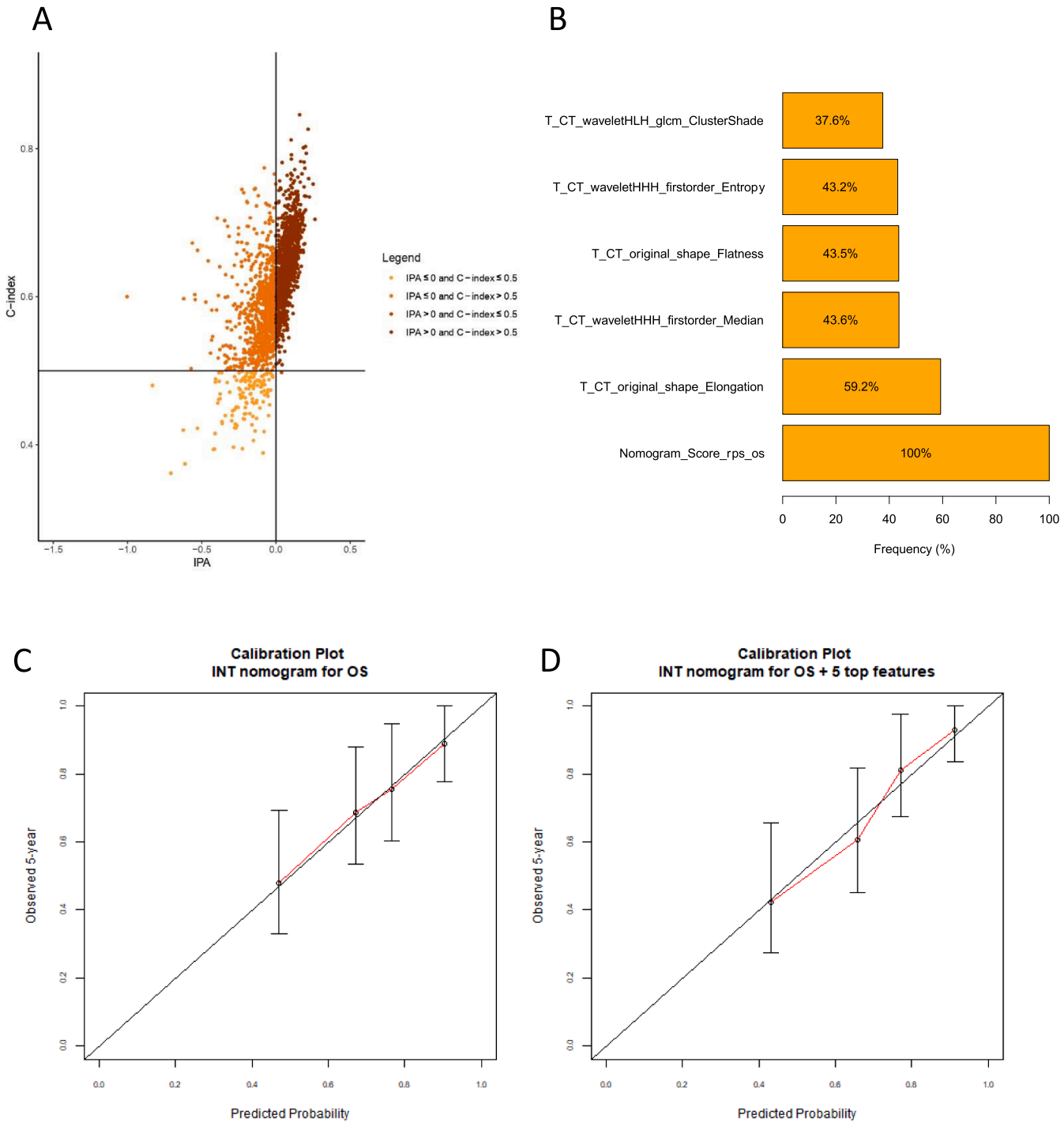

Fig. 4. Results of the random forest-based feature selection for overall survival and calibration of models including the selected features. Panel **A**: scatter plot of IPA (x-axis) and c-index values (y-axis) for each context. Based on these two metrics, contexts were classified as 'non-harmful' (upper right quadrant) and 'harmful' (upper left, lower left, and lower right quadrant). Panel **B**: bar plot showing the proportion of contexts in which the Sarculator and the top five radiomic features were selected. Panel **C**: calibration plot from a Cox model including the Sarculator alone. Panel **D**: calibration plot from a Cox model including the Sarculator and the top five selected radiomic features.

internal validation, which was performed splitting the patient series into two cohorts. Another limitation is the relatively low number of patients, considering that large sample sizes are required to investigate the prognostic relevance of large number of variables [16]. However, these limitations remain intrinsic to the rarity of RPS [17] and this study represents, to the best of our knowledge, the first analysis that investigate the prognostic relevance of CT scan-based radiomic features with special regards to their added value to current patient staging (i.e., Sarculator).

The widespread application of nomograms in clinical practice, which has ultimately led to their integration into the 8th edition of the AJCC staging manual [1], stems from the fact that they utilize variables that are routinely collected as part of standard clinical management [18,19].

Radiomic features constitute another set of information that could be retrieved, as all patients with RPS undergo at least one preoperative CT scan. We observed that radiomics variables obtained from baseline CT

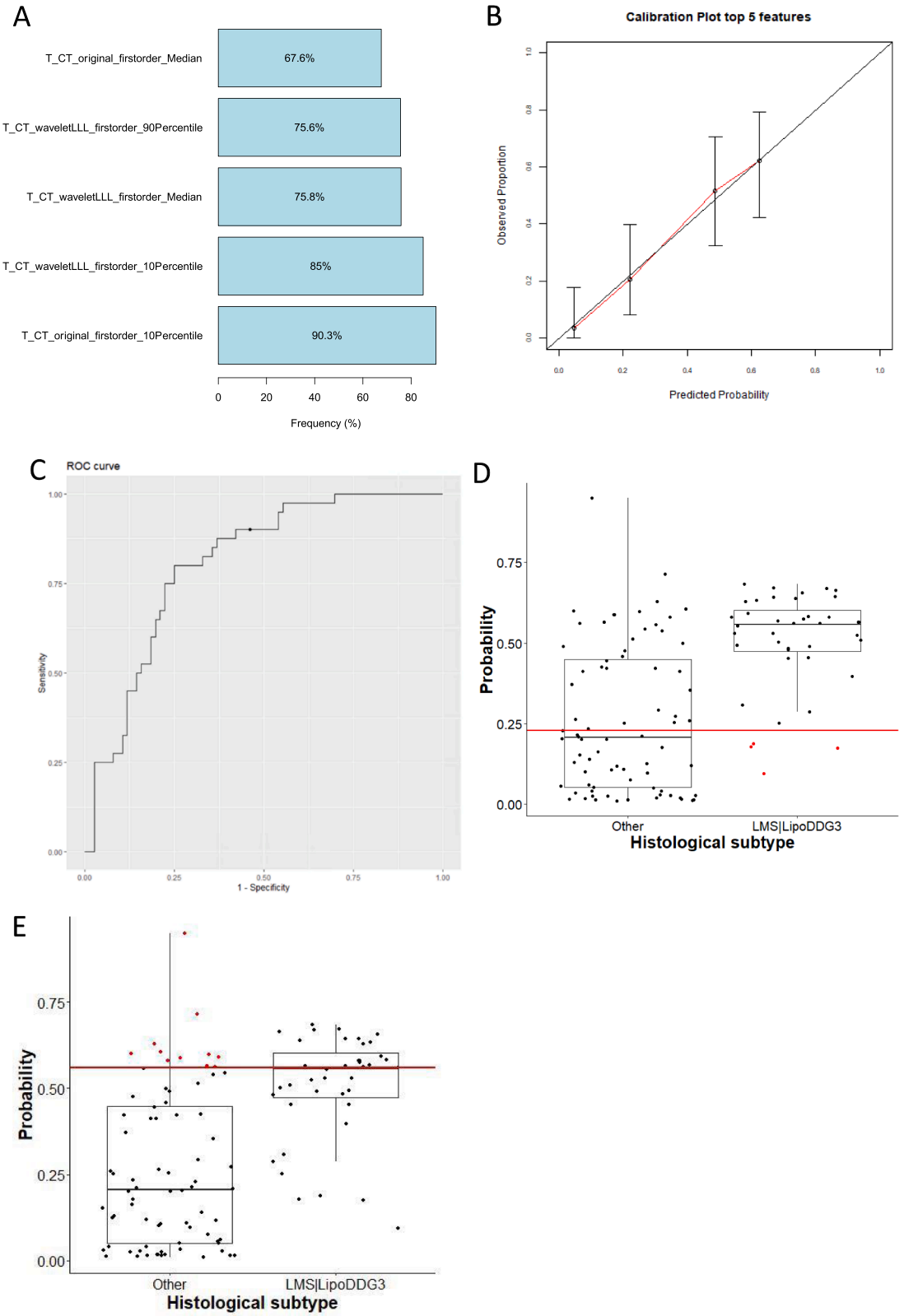

Fig. 5. Results of the random forest-based feature selection for histological subtype classification and calibration of model including the selected features. Panel **A**: bar plot showing the proportion of contexts in which the top five radiomic features were selected. Panel **B**: calibration plot from a binary logistic model including the top five selected radiomic features. Panel Panel C: logistic model generated ROC-curve. Panel **D and E**: box plots showing the distribution of predicted probabilities, derived from a binary logistic model including the top five selected radiomic features, in the two histological subtypes. In panel **D** the red horizontal line represents the cut-point of 0·229 which resulted in 4 FN patients, identified with red dots. In panel **E** the red horizontal line represents the cut-point of 0·5609 which resulted in 11 FP patients, identified with red dots.

scans of patients with primary RPS had limited prognostic potential. The exploitation of baseline CT scans in RPS patients to investigate the association between radiomic features and patient survival is relatively new. In particular, in this study we did not observe a significant advantage in using contrast-enhanced CT scan compared with non-contrast-enhanced CT scan and this might translate into less variation of the results among different institutions. This study showed that radiomics variables, alone, achieved suboptimal discrimination, lower than 0.6, and only marginally improved Sarculator performance in terms of C-index or IPA. However, the marginal improvement in accuracy of patient risk stratification detected in this study should not discourage further investigations. In other cancers, analyses have demonstrated that incorporating information about the tumor's molecular profile can significantly enhance the relevance of radiomic features, emphasizing the complementary value of these data [20–22]. Currently, we are actively working on integrating omic data in the above mentioned SARCOMICS study to test whether this hypothesis holds true in the case of RPS.Compared to previous work reported in literature [23] from Peeken et al, our analysis stands out for its innovative methodology for features extraction and significant homogeneity in acquisition parameters and study population. Additionally, we investigated the clinical utility [24] of adding a radiomic signature to current patient staging, showing its limited added value. Conversely, this study standardized feature variability across sites and cross-validation to select radiomic and clinical features for generalizable survival predictions.

In this study we observed that the use of radiomics to predict specific RPS histologic types demonstrated potentially relevant findings. Our results are consistent with a recent study on two independent cohorts of patients with primary RPS which showed that radiomic features could predict both RPS histology and tumor malignancy grade [12]. However, the study from Arthur et al. analysed only liposarcoma and leiomyosarcoma, two histologies which have distinct radiologic features and for which grade 1 malignancy is applicable predominantly, if not only, to WDLPS. On the contrary, the current study also included patients with histologies other than DDLPS and LMS, increasing the relevance of our findings.

Preoperative biopsies are limited in the definition of tumour malignancy grade, especially for LMS [25] and DDLPS [26], where neoadjuvant chemotherapy is under investigation in the phase III randomized clinical trial STRASS-2. In retroperitoneal DDLPS, a G3 DDLPS is missed in approximately 40 % of patients [26]. In retroperitoneal LMS, G1 tumours are exceedingly rare being the vast majority characterized a malignancy grade 2–3 [25,27]. The top-performing features in our radiomic model, which enabled the identification of G3 DDLPS or LMS, are represented by First Order (FO), also known as intensity features, and Gray Level Co-occurrence Matrix (GLCM). These surrogate variables quantify the spatial distribution and complexity of voxel intensities within the ROI, respectively. We reported a homogeneous distribution of voxel intensities and low spatial complexity within G3 DDLPS or LMS.

In summary, radiomic features marginally enhanced the prognostic risk stratification of Sarculator in patients with RPS. Notably, these features could be leveraged to pinpoint patients with LMS and G3 DDLPS. Despite the internal validation conducted in this study, independent validation in prospective series is essential to establish radiomic features as candidates for refining Sarculator and identifying patients with G3 DDLPS or LMS, which could inform the need for preoperative chemotherapy to lower their risk of mortality. Furthermore, integrating genomic and transcriptomic data holds promise for further elevating the prognostic and predictive accuracy of radiomic features within the Sarculator.

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CRediT authorship contribution statement

Gabriele Infante: Writing – review & editing, Formal analysis, Data curation. **Roberta Sanfilippo:** Writing – review & editing. **Andrea Vanzulli:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Paola Collini:** Writing – review & editing. **Sara Iadecola:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Viviana Vallacchi:** Writing – review & editing. **Sandro Pasquali:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Dario Callegaro:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Stefano Percio:** Writing – review & editing, Data curation. **Alessandro Gronchi:** Writing – review & editing, Investigation, Conceptualization. **Alessia Beretta:** Writing – review & editing, Data curation. **Rosalba Miceli:** Writing – review & editing, Supervision, Formal analysis. **Carlo Morosi:** Writing – review & editing, Data curation. **Luca Mainardi:** Writing – review & editing, Supervision. **Raffaella Vigorito:** Writing – review & editing, Data curation. **Matteo Benelli:** Writing – review & editing, Supervision. **Paul Huang:** Writing – review & editing. **Gabriella Francesca Greco:** Writing – review & editing, Data curation. **Marco Fiore:** Writing – review & editing. **Valentina Corino:** Writing – review & editing, Writing – original draft, Data curation. **Silvia Stacchiotti:** Writing – review & editing. **Marco Bologna:** Writing – review & editing, Writing – original draft, Data curation. **Chiara Fabbroni:** Writing – review & editing.

Declaration of Competing Interest

The authors reported no conflict of interest related to the content of this manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115120.

Data Availability

The data analyzed in the present manuscript are available at https://zenodo.org/records/10696131.

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