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Original Research

Machine learning and natural language processing (NLP) approach to predict early progression to first-line treatment in real-world hormone receptor-positive (HR+)/HER2-negative advanced breast cancer patients

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Abstract ***Background:*** CDK4/6 inhibitors plus endocrine therapies are the current standard of care in the first-line treatment of HR+/HER2-negative metastatic breast cancer, but there are no well-established clinical or molecular predictive factors for patient response. In the era of personalised oncology, new approaches for developing predictive models of response are needed.

Materials and methods: Data derived from the electronic health records (EHRs) of real-world patients with HR+/HER2-negative advanced breast cancer were used to develop predictive models for early and late progression to first-line treatment. Two machine learning approaches were used: a classic approach using a data set of manually extracted features from reviewed (EHR) patients, and a second approach using natural language processing (NLP) of free-text clinical notes recorded during medical visits.

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Results: Of the 610 patients included, there were 473 (77.5%) progressions to first-line treatment, of which 126 (20.6%) occurred within the first 6 months. There were 152 patients (24.9%) who showed no disease progression before 28 months from the onset of first-line treatment. The best predictive model for early progression using the manually extracted dataset achieved an area under the curve (AUC) of 0.734 (95% CI 0.687–0.782). Using the NLP free-text processing approach, the best model obtained an AUC of 0.758 (95% CI 0.714–0.800). The best model to predict long responders using manually extracted data obtained an AUC of 0.669 (95% CI 0.608–0.730). With NLP free-text processing, the best model attained an AUC of 0.752 (95% CI 0.705–0.799).

Conclusions: Using machine learning methods, we developed predictive models for early and late progression to first-line treatment of HR+/HER2-negative metastatic breast cancer, also finding that NLP-based machine learning models are slightly better than predictive models based on manually obtained data.

1. Introduction

The treatment of HR+/HER2-negative metastatic breast cancer has drastically improved with the approval of cyclin-dependent kinase (CDK) 4 and 6 inhibitors. Data from pivotal trials assessing combinations of different CDK4/6 inhibitors plus endocrine therapies (ET) have shown concordant results with regard to progression-free survival (PFS) in the first-line treatment of both postmenopausal [1–6] and premenopausal [7–9] patients. The addition of CDK4/6 inhibitors increases the median PFS in the first-line setting by 60–90% compared to that obtained with ET alone. This benefit was found to be maintained in all subgroups analysed according to the location of the disease, previous neoadjuvant and adjuvant treatments, number of metastatic sites, age, ECOG or time elapsed from the end of hormone adjuvant treatment until the diagnosis of distant recurrence.

All of the variables mentioned above are considered prognostic factors for overall survival in patients with metastatic breast cancer, as verified in different series of patients [10–15]. Although it could be assumed that these prognostic factors are also prognostic for PFS in first-line treatment for metastatic disease, there are no specific data to confirm this point. In fact, available data indicate that PFS and overall survival are only moderately correlated in metastatic breast cancer [16]. Furthermore, it is possible that other variables collected in medical records could be useful for the definition of PFS prognostic patient subgroups.

In the current context of advanced breast cancer management, treatments should be personalised and indicate a certain treatment in those patients with the greatest expected benefit. Therefore, it is of considerable interest to define different subgroups of patients with different risks of progression to first-line treatment for metastatic disease in order to be able to select the best therapeutic option with the greatest accuracy and efficiency.

In recent years, artificial intelligence (AI) has begun revolutionising several industries, including healthcare. Healthcare delivery organisations have invested a considerable amount of time and effort in the development of AI driven medical tools and research. The goal of applying machine learning, a branch of AI, is to identify patterns in data in order to find a model that best generalises beyond the data seen. Although it is intimately connected to traditional statistical methods, machine learning often seeks nonlinear relationships among the independent variables. In the traditional approach of data analysis one begins with a statistical model, with the data as input to the computation; whereas machine learning differs since it is a data-driven approach that generalises a model from the data in order to obtain a model that can be applied to new data [17].

Electronic health records (EHRs) include large amounts of data from real-world patients collected during regular clinical practice. Although most of these data are recorded in an unstructured text form, the application of machine learning techniques enables the implementation of algorithms to classify features or predict events based on these clinical text notes. Moreover, it is possible to obtain information to identify patients with higher sensitivity and specificity, even more so than that obtained from structured data [18,19]. Furthermore, these techniques have been applied to diagnostic specialties [20,21] and to predict events in cancer patients [22–24].

Our aim was to develop a machine learning model to predict early progression to first-line treatment in metastatic HR+/HER2-negative breast cancer through natural language processing (NLP)-based analysis of free-text clinical notes from EHRs and predict the risk according to the different treatments used in this setting.

In addition, we evaluate if the performance of such model is at least the same as that obtained through the traditional approach using information structured within a database. To further verify the validity of this approach, we also set out to develop a predictive model for long-term responders to first-line treatment, as this is also an important issue to consider when deciding initial therapy.

2. Materials and methods

2.1. Data source and patient selection

This is an observational and longitudinal study in which the data were derived from the EHRs of patients with metastatic HR+/HER2-negative breast cancer treated at Hospital Regional Universitario and Hospital Universitario Virgen de la Victoria in Malaga (Spain). Both hospitals use the same information system called Galen, comprising a database of patients and their EHRs, among other utilities [25]. The EHRs from patients who had received at least one line of treatment between 1991 and 2019 were identified from the database, and those patients with clinical notes in their EHR were included in the study. The EHR contains both structured and unstructured data. The structured fields comprise demographic data, first symptom date, first diagnosis date, tumour characteristics at initial breast cancer diagnosis (histology, tumour size, nodal status, stage), first treatment date, type and intention of first treatment, last control date and last control status. The unstructured data consist of free-text clinical notes recorded by the oncologist at each medical visit. In the development of the machine learning model, all the EHR clinical notes collected up to the start date of the first-line treatment were used, because this information is available in clinical practice when deciding the best therapeutic option for a patient.

Patient data were de-identified. This study was approved by the local research ethics committee.

2.2. Outcomes of interest

Two outcomes of interest were considered. The first one was early progression within 6 months after the first-line treatment. The second outcome was late progression after 28 months of starting the first-line treatment. This cut-off was chosen because it was the median PFS reported in a pooled analysis of patients treated with CDK4/6 inhibitors plus aromatase [26].

2.3. Expert-reviewed patient dataset

Two certified medical oncologists (NR, BJ) manually reviewed de-identified EHR from selected patients. This dataset includes 43 variables covering demographic data, first symptom date, first diagnosis date, tumour characteristics at initial breast cancer diagnosis, first treatment date, details of first treatment, recurrence date, recurrence disease characteristics, first-line treatment, second disease progression date, last control date, and last control status (Supplementary Table S1). First-line treatments were categorised into four groups: chemotherapy (CT) alone, CT plus maintenance ET, ET alone, and ET plus CDK4/6 inhibitors. This dataset was used to develop the predictive model through the classic approach. It was also used in a supervised manner to verify the accuracy of the predictive machine learning model developed from the unstructured free text.

2.4. Model building and validation

The first step was to collect the Spanish free-text clinical notes to generate a text corpus (i.e., a large structured set of texts) from the information stored within the Galen system.

We proceeded to the text processing step after having gathered a corpus of Spanish documents. This step comprises the following tasks: (1) remove irrelevant words and characters, (2) convert all characters to lowercase, (3) combine some misspelled or alternately spelled words into a single representation, and (4) stemming. This last step reduces inflectional and sometimes derivationally related forms of a word into a common base form by removing suffixes or prefixes used with a word.

Subsequently, we needed to represent these preprocessed text documents with a numeric representation as machine learning models take numerical values as input. To achieve this, we proceeded to build a vocabulary of all the unique words in our dataset and associate a unique index to each term. Thus, each text document was represented as a list of indexes as long as the number of distinct words in the text. These lists were used to generate a Document-Term Matrix (DTM), used to store a statistical measure that represents the relevance of a word to a document. The numerical representation of this text ignores the order of words in the documents and is known as a BoW model [27].

Having populated the BoW model with one of the previous statistical measures, we arrived at one of the challenges of this modelling approach: the vast number of features. Accordingly, we applied different feature selection methods to reduce the dimensionality of our dataset. The selected methods applied were (1) Analysis of Variance (ANOVA), (2) Levene's Test, (3) Correlation-Based Feature Selection (CFS), and (4) Principal Component Analysis (PCA).

Afterwards, we proceeded to feed the filtered dataset into fold cross validation of 10 folds in order to perform a robust estimation of the prediction error because in real-world problems, they cannot be exactly calculated. This technique divides the dataset into k folds, creates a classifier using k-1 fold for training, and an error value is

calculated by testing the classifier in the remaining fold. Then the error is estimated by taking the average value of the error for each fold [28], thus enabling the performance assessment of the following machine learning algorithms: Naive Bayes (NB), Linear Discriminant Analysis (LDA), Decision Trees (DT), Support Vector Machines (SVM), Lasso Regression, Ridge Regression, Elastic Net, Generalized Linear Boosting (GLMBoost), Adaptive Boosting (ADA), Gradient Boosting Machine (GBM), Bayesian Additive Regression Trees (BART), and Random Forests (RF) [29].

To evaluate the quality of these estimates, we applied a robust inference based on resampling methods [30] in order to obtain confidence intervals for the cross-validation AUC results. To establish statistically significant differences between the models, the non-parametric Wilcoxon signed-rank test was employed to compare the distribution of pairwise cross-validation AUC values [31].

We performed all statistical analysis using R version 3.6.1 and Python version 3.7.6.

3. Results

3.1. Cohort characteristics

Of the 665 patients diagnosed with HR+/HER2- negative advanced breast cancer during the study period, 55 were excluded from the study because the follow-up period after the onset of first-line treatment was shorter than 6 months. Thus, 610 patients were included in the final analysis, with a total of 17,426 clinical visits from which free-text notes were collected. The median follow-up for metastatic disease of the whole cohort was 32.2 months. When considering each group, the mean follow-up period was 39.8 months for ET treatment, 36.3 months for CT plus maintenance ET, 19.7 months for CT alone, and 18.7 months for ET plus CDK4/6 inhibitors.

The mean age of patients was 52 years (range 22–89 years) and 23.4% were classified as stage IV at diagnosis (Table 1). Regarding the classification of tumours, 19.5% were luminal A due to a Ki67 value <14%, 37.2% were luminal B, and the Ki67 value was unknown in 43.3% of cases. Approximately half (51%) of the patients were treated with ET, 19.5% received CT alone, 19.2% were treated with CT plus maintenance ET, and 10.3% with ET plus CDK4/6 inhibitors.

There were 473 (77.5%) progressions to first-line treatment, with 126 (20.6%) occurring within the first 6 months. Of these early progressions, 57 patients had received ET (9.3%), 54 CT (8.9%), 4 CT plus ET maintenance (0.7%), and 11 ET plus CDK4/6 inhibitors (1.8%).

There were 152 long-responder patients (24.9%) in our cohort, who did not show disease progression earlier than 28 months from the onset of first-line treatment. Of these patients, 103 had been treated with ET (16.9%), 9 with CT (1.5%), 37 with CT plus maintenance ET (6.1%), and 3 with ET plus CDK4/6 inhibitors (0.5%).

Table 1
Patient characteristics.

Characteristic	n
N	610
Medical encounters analysed	17,426
Age at diagnosis (years; median, range)	52 (22–89)
Menopausal status at diagnosis	
Premenopausal	297 (48.7%)
Postmenopausal	272 (44.6%)
Unknown	41 (6.7%)
Stage at diagnosis	
I	60 (9.8%)
II	198 (32.5%)
III	186 (30.5%)
IV	143 (23.4%)
Unknown	23 (3.8%)
Grade at diagnosis	
1	63 (10.3%)
2	244 (40.0%)
3	122 (20.0%)
Unknown	181 (29.7%)
Neo/adjuvant chemotherapy	
Anthracyclines	119 (19.5%)
Anthracyclines-taxanes	168 (27.5%)
Taxanes	5 (0.8%)
CMF	57 (9.3%)
Unknown	16 (2.6%)
No chemotherapy	245 (40.2%)
Adjuvant hormone therapy	
Tamoxifen	279 (45.7%)
Aromatase inhibitors	59 (9.7%)
Tamoxifen-aromatase inhibitors	61 (10.0%)
Unknown	11 (1.8%)
IHQ phenotype	
Luminal A	119 (19.5%)
Luminal B	227 (37.2%)
Luminal unknown	264 (43.3)
IHQ, immunohistochemical.	
First-line treatment	
Hormone therapy	311 (51.0%)
Hormone therapy plus CDKI4/6 inhibitors	63 (10.3%)
Chemotherapy	119 (19.5%)
Chemotherapy plus ET maintenance	117 (19.2%)
First-line treatment total progressions	
Hormone therapy	246 (40.3%)
Hormone therapy plus CDKI4/6 inhibitors	34 (5.6%)
Chemotherapy	102 (16.7%)
Chemotherapy plus ET maintenance	91 (14.9%)
First-line treatment early progressions	
Hormone therapy	57 (9.3%)
Hormone therapy plus CDKI4/6 inhibitors	11 (1.8%)
Chemotherapy	54 (8.9%)
Chemotherapy plus ET maintenance	4 (0.7%)
First-line treatment long-responders	
Hormone therapy	103 (16.9%)
Hormone therapy plus CDKI4/6 inhibitors	3 (0.5%)
Chemotherapy	9 (1.5%)
Chemotherapy plus ET maintenance	37 (6.1%)
ET, Endocrine therapy.	

Table 2
Performance metrics of machine learning models.

	Dataset	Best model	AUC (95% CI)	TPR (95% CI)	TNR (95% CI)
Early progressions	Manually extracted	Elastic Net	0.734 (0.687–0.782)	0.736 (0.729–0.743)	0.713 (0.707–0.719)
	NLP	GLMBoost	0.758 (0.714–0.800)	0.758 (0.751–0.764)	0.707 (0.701–0.714)
Long responders	Manually extracted	Elastic Net	0.669 (0.608–0.730)	0.664 (0.654–0.674)	0.658 (0.649–0.667)
	NLP	GBM	0.752 (0.705–0.799)	0.717 (0.710–0.723)	0.766 (0.760–0.773)

AUC, area under the curve; NLP, natural language processing; TPR, true positive rate; TNR, true negative rate.

3.2. Model performance for early progressions

Using the dataset of manually extracted features of the reviewed patients, the model that yielded the best result was Elastic Net, which showed an AUC of 0.734 (95% CI 0.687–0.782). With the NLP free-text processing approach, the best model was GLMBoost, achieving an AUC of 0.758 (95% CI 0.714–0.800) (Table 2). Fig. 1 shows an example of the report obtained when predicting the early progressions for each of the proposed treatments.

3.3. Model performance for long responders

The algorithm that showed best performance for predicting long responses with the dataset of manually extracted patient features was Elastic Net, which obtained an AUC of 0.669 (95% CI 0.608–0.730). With the NLP free-text processing approach, GBM was the most relevant algorithm, attaining an AUC of 0.752 (95% CI 0.705–0.799) (Table 2). Fig. 2 shows an example of the report obtained when predicting long-duration responses.

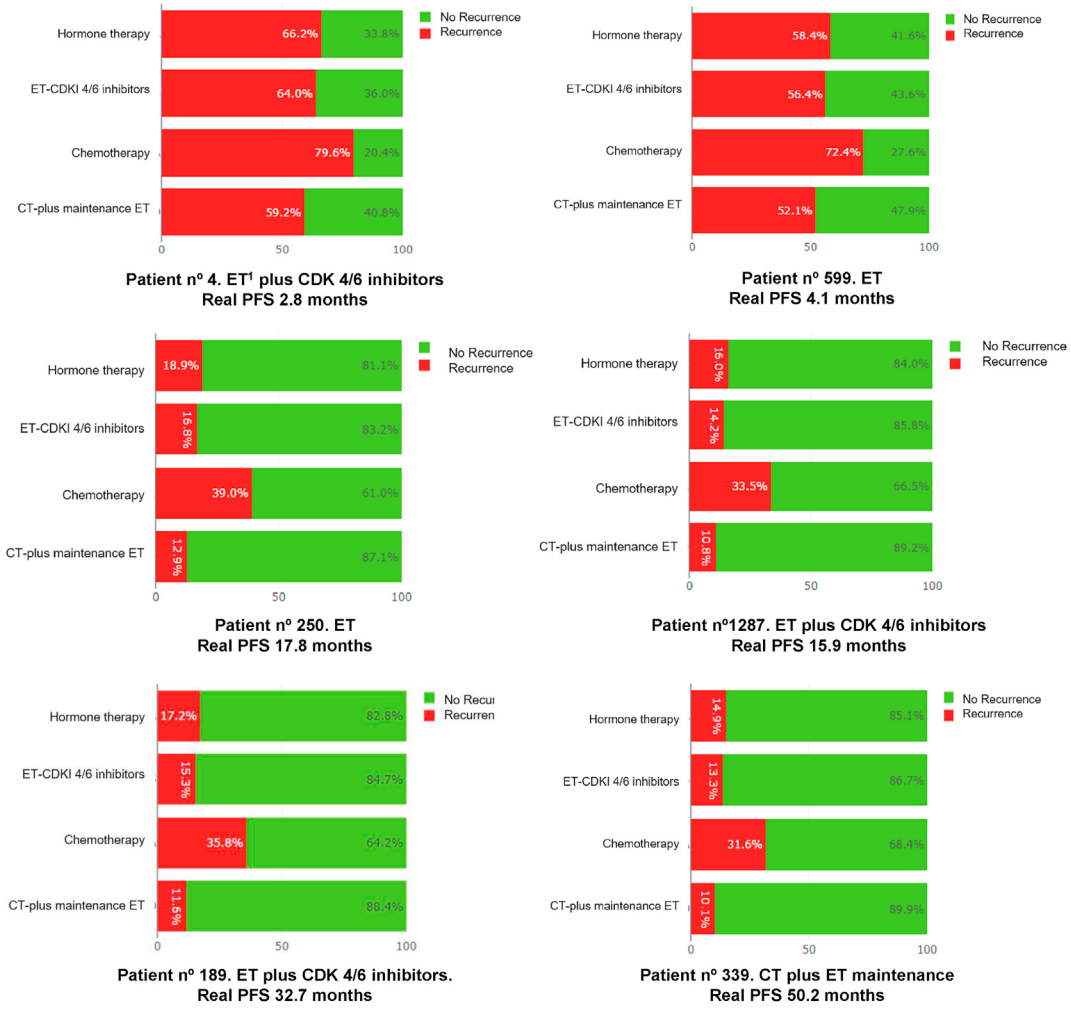

Fig. 1. This figure shows some examples of the application of our predictive model in real patients. The coloured areas show the risk of presenting (red) or not presenting (green) an early recurrence for each of the therapeutic options. The type of treatment the patient received and the progression-free survival obtained with the first-line treatment are indicated in bold. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

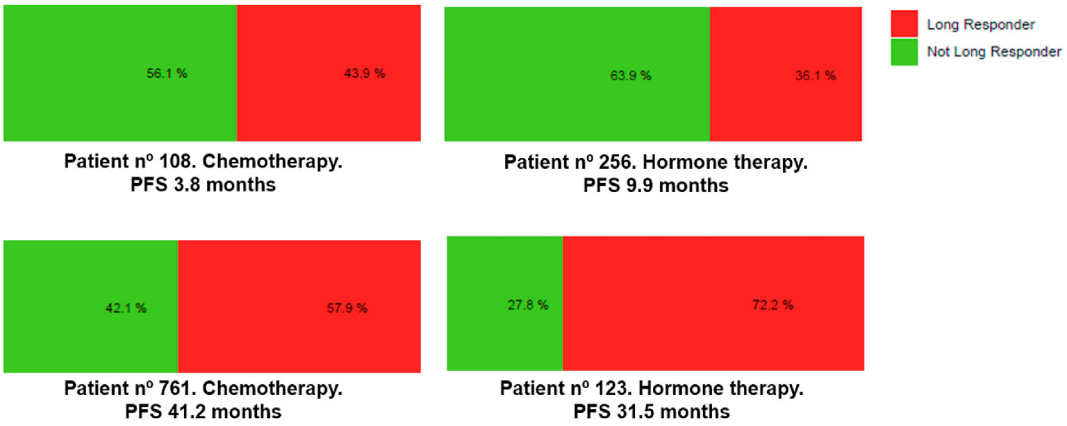

Fig. 2. This figure displays some examples of the application of our predictive model in real patients. The coloured areas show the likelihood of being a long responder (red) or not (green) with the first-line treatment (i.e., progression-free survival >28 months). The type of treatment the patient received and the progression-free survival achieved with the first-line treatment appears in bold. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

The treatment of HR+/HER2-negative metastatic breast cancer has evolved substantially in recent years, and will certainly continue to do so in the future [32,33]. However, we do not currently have robust predictive factors to help choose the best treatment in a specific patient in daily practice, and attempts to identify predictive molecular factors have not yielded the desired results [34,35]. In this context, new approaches for developing predictive models of patients' response to different available therapeutic options are needed.

The innovation and development of artificial intelligence medical tools and research are able to provide effective and efficient predictive models that improve the generalisation capacity of traditional statistical models, since they are capable of capturing complex relationships between the prognostic factors and the study variables. However, although these tools are very valuable, they require time and computational resources to develop, in addition to the interpretation difficulties as the models are more complex. Thus, additional techniques are required to extract valuable information and insight from the models, also known as explainable machine learning.

We developed a machine learning predictive model for early progression to first-line treatment of patients with HR+/HER2-negative advanced breast cancer based on analysis of the unstructured information contained in the free-text notes of EHRs using NLP techniques. Using the same methodology, we were also able to develop a predictive model to identify long-responder patients. Our approach used the information collected during medical visits as a whole, without the need to transform it into structured data for analysis. To the best of our knowledge, our study is the first application of NLP techniques in the development of a predictive model for breast cancer in this setting. Other authors have used machine learning approaches to predict the efficacy of CDK4/6 inhibitors in HR+/HER2-negative metastatic breast cancer [36]. Patient data pooled from 8 clinical trials were included in the study, but only structured characteristics of the disease and baseline patient status were analysed. The CDK4/6 inhibitor model produced a prediction accuracy of 69.2%, and the ET alone model had an accuracy of 70.6%. Machine learning methods have also been used to develop predictive models to address other issues but transforming EHR information into structured variables [23,24,37]. Moreover, our results demonstrate that NLP-based machine learning models are slightly better at predicting early and late events than manually curated data-based predictive models. The relevance of this type of model is noteworthy, as they improve the predictive capacity by highlighting details not revealed by classic manual extraction [22]. Furthermore, the efficiency is increased by reducing the time and expense required to review medical records [38]. Likewise, another strength of our model is that it is developed from real-world patients. Interest in the use of data obtained from real-world patients is growing as it provides information from a much broader population than that included in clinical trials, and is therefore more relevant from a healthcare point of view [39].

Our study has several limitations. As it is a retrospective study of two unique institutions, it is possible that there were data selection, measurement biases, and missing data. Regarding the laboratory and pathology reports, only the information entered into the EHR by the oncologist was used. It is possible that the use of original reports may have influenced the results of our predictive model. Although our model was subjected to an accurate internal validation process, it is necessary to verify that it can be applied to other patients with other

EHRs through appropriate external validation. In addition, we were unable to adjust the model to predict the risk of early progression for each of the 4 categories of treatment with enough accuracy to be clinically relevant. The low number of patients and the somewhat short length of follow-up in each of the categories contributed to this issue. For example, the number of patients treated with ET plus CDKI was 63 and the median follow-up for metastatic disease of these patients was 18.7 months.

In conclusion, we successfully developed a NLP-based machine learning model to predict 2 very different types of events (i.e., early progression and long responders) that are of great importance when deciding the best therapeutic approach for patients with metastatic HR+/HER2-negative breast cancer.

Author contributions

N.R., J.M.J., E.A: Study concepts. N.R., J.M.J., P.R-B., H.M., L.F., E.A.: Study design. N.R., J.M.J., P.R-B., B.J., T.D-R., H.M., A.M., A.S-M., B.P., F.C., M.J.B., E.V., M.E.D-R, E.S., L.G., A.G., S.R-M., I.L., E.A.: Data acquisition. J.M.J., P.R-B., H.M., L.F.: Quality control of data and algorithms. N.R., J.M.J., P.R-B., H.M., E.A.: Data analysis and interpretation. N.R., J.M.J., P.R-B., H.M., E.A.: Statistical analysis. N.R., J.M.J., P.R-B., E.A.: Manuscript preparation. N.R., J.M.J., P.R-B., E.A.: Manuscript editing. N.R., J.M.J., P.R-B., B.J., T.D-R., H.M., A.M., A.S-M., B.P., F.C., M.J.B., E.V., M.E.D-R, E.S., L.G., A.G., L.F., S.R-M., I.L., E.A.: Manuscript review.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.11.030.

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