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Table 1 is available in the Supplementary Files section

Supplementary Tables S1-S2 are not available with this version
Estimated survival outcomes and absolute chemotherapy treatment benefit using PREDICT Tool® and EndoPredict®, in hormone-positive early-stage breast cancer.

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ABSTRACT

INTRODUCTION: PREDICT is an online tool that estimates the 10-year breast cancer overall survival (10OS) with different adjuvant treatment combination. EndoPredict® is a genetic biomarker to guide decision on adjuvant systemic therapy in hormone-positive early-stage breast cancer. No study had ever correlated the estimated outcomes of PREDICT and EndoPredict® results.

MATERIAL AND METHODS: We collected data of 249 patients with a 12-gene molecular test (EndoPredict®). EndoPredict® risk-score (EPclin) categorized patients in low (EPclin < 3.3) or high-risk (EPclin ≥ 3.3) of recurrence. The benefit of chemotherapy and the overall survival at 10 years (10OS) with endocrine therapy alone or with chemoendocrine therapy was estimated with PREDICT.

RESULTS: From March 2017 to May 2022, 249 EndoPredict® tests (39% low-risk EPclin and 61% high-risk EPclin) were evaluated. In high-risk EPclin population compared with low-risk EPclin, 15% vs 6% (p=0.047) had a previous breast cancer event, 31% vs 14% a total mastectomy (p=0.006), 23% vs 10% do not express the progesterone receptor (p=0.011), 11% vs 5% had a SBR grade III (p=0.004) and 84% vs 63% had a Ki67 higher than 10% (p<0.001). The median estimated 10OS was prolonged by chemoendocrine therapy (85%) compared with endocrine therapy alone (83%) in high-risk EPclin (p=0.02), without difference in low-risk EPclin. The median chemotherapy benefit at 10OS was 2% [0.5-5.9] for low-risk and 2.6% [0.7-7.5] for high-risk EPclin (p = 0.0001).

CONCLUSION: EPclin seemed to be a predictive factor of adjuvant chemotherapy at 10OS. Results of prospective trials UNIRAD and RESCUE are pending.

INTRODUCTION

Early-stage hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer is the most common type of breast cancer¹. Adjuvant chemotherapy combined to endocrine therapy reduce the risk of recurrence². However, the majority of patients may receive chemotherapy unnecessarily. Clinicopathological features including, tumor size, histologic grade, the presence of axillary lymph-node metastases, Ki67 status help the decision. To personalize breast cancer treatment, several prediction tools have been developed including PREDICT tool (PREDICT).

Available on the website, PREDICT estimates the 10-year overall survival (10OS) for women surviving five years with the benefit of 5 years of hormone therapy and taxane-based adjuvant chemotherapy. The benefit of radiotherapy and the recurrence of disease was not able in this currently version³.
In 2016, several commercially available genomic tests have been developed in ER-positive, HER2-negative breast cancer in addition to conventional markers. The application of genetic signatures contributes to determine a less toxic adjuvant treatment by foregoing chemotherapy. Two large randomized phase III trials, ABCSG6 and ABCSG8, as well as premenopausal patients study validated EndoPredict® test as an independent predictor of distant recurrence in node-negative and node-positive breast cancer.

EndoPredict® test may identify women with 0-3 positive nodes who have low enough risk of distant recurrence at 10 years and can be treated with 5 years of endocrine therapy alone. In ABCSG 6/8 cohort, EndoPredict® test was evaluated in 1,702 women with ER-positive, HER2-negative breast cancer who received 5 years of endocrine therapy alone. Of those, 77.8% of patients had node-negative disease and 35% of patients had 1-3 positive nodes. The 10-year distant recurrence-free rates for patients with low-risk EndoPredict® risk-score (EPclin) were 95.5% (94% to 97.1%) with node-negative disease and 95.6% (92.2 to 99.1%) with 1-3 positive nodes.

High-risk EndoPredict® test score could predict chemotherapy benefit in women with ER-positive, HER2-negative disease. A comparative, nonrandomized analysis of EPclin in women who received adjuvant endocrine therapy alone (ABCSG 6/8, TransATAC) compared with those receiving chemoendocrine therapy (GEICAM 2003-02/9906) was performed to determine the predictive power of EPclin for chemotherapy benefit. In 3,746 women, those with high-risk EPclin had a significant improvement in 10-year distant recurrence free interval with the addition of chemotherapy to endocrine therapy (12% vs 20%).

2022 French guidelines recommend to prescribe genomic tests based on the absolute 10-year survival chemotherapy benefit according to PREDICT: < 2% chemotherapy is not recommended; 2-5% chemotherapy benefit is uncertain and a genetic signature is recommended; > 5% chemotherapy is recommended. No study evaluated the overall survival benefit of chemotherapy according to EPclin.

From March 2017 to November 2021, EndoPredict® tests were respectively used in our institution. The aim of this study was to evaluate the estimated PREDICT survival outcome according to EndoPredict® test results.

**MATERIAL AND METHODS**

**Patients**

Institutional review board approval was obtained to conduct this study. Retrospectively, patients with an EndoPredict® test from our center have been included. All patients had a biopsy-proven HER2-negative, HR-positive breast cancer carcinoma followed by a breast cancer surgery. Patients with evidence of metastatic stage at the computed tomography scan or the positron emission tomography scan, or a HER2-positive breast cancer, or a bilateral synchronous breast cancer or a missing EndoPredict® test were excluded. Adjuvant chemotherapy, endocrine therapy and radiation therapy were prescribed at the discretion of the treating physicians.

**Study outcomes**

**EndoPredict®**

**EndoPredict® risk-score**

The 12-gene expression assay was performed in our local laboratory. The ribonucleic acid (RNA) expression of 8 target genes (BIRC5, DHCRT7, UBE2C, AZGP1, IL6ST, MGP, RBBP8, STC2) and 3 normalization genes (CALM2, OAZ1, RPL37A) was measured by real-time reverse transcription-polymerase chain reaction (RT-PCR). EPclin, combined molecular and clinical risk-score, was calculated by combining the 12-gene molecular score with tumor size and the number of positive lymph node.
Tumors with an EPclin score <3.3 were considered low risk for distant recurrence and tumors with score ≥ 3.3 were considered high risk for distant recurrence.

Predictive survival and chemotherapy benefit

PREDICT version 1 was developed using cancer registry data from United Kingdom on 5,694 women from 1999 to 2003 with a median length of follow-up of 5.6 years. The Ki67 status was added in version 1.2 but was still underestimate breast cancer specific mortality in women diagnosed under the age of 40. In order to take into account age at diagnosis and smooth out the survival function for tumor size and node status, PREDICT version 2.0 was re-fitting adding 3787 women with 10 years of follow-up. The version 2.1 was corrected for older women for which PREDICT overestimated the benefit of adjuvant treatment. Actually, in PREDICT version 2.2 was added an option for estimating the survival outcome of extended hormone therapy according to ATLAS\textsuperscript{13} and aTTom\textsuperscript{14} trials.

From clinicopathological features, PREDICT version 2.2 (PREDICT), was available on the website https://breast.predict.nhs.uk. PREDICT used data about the survival of similar women in the past to show the likely proportion of such women expected to survive up to 10 years after their surgery with different treatment combinations.

The estimated 10OS for each patient was defined by the percentage of patients who survive at least 10 years after surgery (i) without adjuvant treatment; (ii) with 5-year endocrine therapy alone; (iii) with 5-year endocrine and third-generation chemotherapy drug regimens that contain taxanes such as paclitaxel and docetaxel.

The estimated magnitude of benefit of endocrine therapy plus chemotherapy compared to endocrine therapy alone for 10OS defined the additional chemotherapy benefit at 10OS.

Statistics

Data were analyzed using the R 3.5.1 Windows software. The description of the study population and the different parameters consisted of absolute and relative frequencies for qualitative data, and descriptive statistics such as median and range for quantitative data. Box-plots and scatter plot were drawn with Microsoft Excel® software.

Univariate analyses were performed to compared low and high-risk EPclin population. T-Student test were performed to compared qualitative and quantitative data with a significant p-value < 5%.

RESULTS

Patients, tumor characteristics

Between March 2017 to May 2022, 271 patients had done an EndoPredict® test. 22 patients were excluded, 12 had a synchronous bilateral breast cancer, 7 had a metastatic breast cancer, 2 had a overexpression of HER2 breast cancer and 1 EndoPredict® test was not evaluable. 249 patients were analyzed.

Patients and tumor characteristics are reported in (Table 1).

The population had a median age of 62 years and was predominantly female (99%), postmenopausal (73%) at the time of diagnosis. 29 patients had a previous history of breast cancer, 23 of which had a high-risk EPclin. Most of patients had a grade II SBR (78%) without axillary lymph nodes involvement (72%). The estimated magnitude of benefit of chemotherapy according to PREDICT was mostly ranged from 2% to 5% (63%).

Patients with low and high-risk EPclin were evaluated separately. 61% had a high-risk EPclin and 39% had a low-risk EPclin. Compared with low-risk EPclin population, high-risk EPclin had 15% vs 6% of
previous breast cancer event \((p=0.047)\), 31% vs 14% total mastectomy \((p=0.006)\), 23% vs 10% do not express the progesterone receptor \((p=0.011)\), 11% vs 5% had a SBR grade III \((p=0.004)\) and 84% vs 63% had a Ki67 higher than 10% \((p<0.001)\). There was no difference in both groups for node invasion \((p=0.55)\). Univariate analyses are summarized in the Data Supplement \((Table S1)\).

For patients with an estimated adjuvant chemotherapy benefit between 1% and 5% according to PREDICT, EndoPredict® categorized them into low-risk and high-risk distant recurrence.

The estimated magnitude of benefit of chemotherapy at 10OS in low and high-risk EPclin was reported in Figure 1. Between 1% to 3% of chemotherapy benefit, 89 (40%) patients had a low-risk EPclin and 132 (60%) a high-risk EPclin. Between 3.1% to 5% of chemotherapy benefit, 7 (12%) patients had a low-risk EPclin and 50 (88%) patients had a high-risk EPclin.

Among 92 patients with an absolute 10OS benefit chemotherapy less than 2%, 37 (40%) had a high-risk EPclin \((Table S2)\). However, only 8 patients had an absolute 10OS benefit chemotherapy more than 5% with 2 patients with low-risk EPclin.

EndoPredict®: a predictive factor for adjuvant chemotherapy benefit at 10OS estimated by PREDICT.

The estimated 10OS according to different adjuvant combination treatments and EPclin was reported in Figure 2. EPclin was a significant predictor of adjuvant chemotherapy at 10OS for high-risk EPclin.

In low-risk EPclin group, the median estimated 10OS was not prolonged by adjuvant chemotherapy treatment: 83% [40-94] without chemotherapy treatment compared with 85% [42-95] with adjuvant chemotherapy \((p = 0.17)\).

In high-risk EPclin group, the median estimated 10OS was prolonged by adjuvant chemotherapy treatment: 82% [45-94] without chemotherapy treatment compared with 85% [46-95] \((p= 0.02)\).

The distribution of high and low-risk EPclin according to estimated magnitude of benefit of adjuvant chemotherapy at 10OS was reported in Figure 3.

The adjuvant chemotherapy benefit at 10OS in high-risk EPclin group was higher than the low-risk group \((p<0.0001)\). The median chemotherapy benefit at 10OS was 2% [0.5-5.9] for low-risk EPclin and 2.6% [0.7-7.5] for high-risk EPclin.

**DISCUSSION**

PREDICT predicts overall survival reliably in patients RH-positive and tumor size under 5cm (T3)\(^15\). Several studies consider a difference between predicted and observed outcomes of less than 2% as accurate\(^16,17\). However, PREDICT tends to underestimate mortality for young patients under 40-year-old and overestimate 10 years overall survival in older patients\(^18,19\). Consequently, the prediction of 10OS was reliable in this study with few patients with extreme age and few tumor sizes over 5cm. However, the presence of lymphatic or vascular invasion was an important factor used to select patients for systemic therapy\(^20\) and could underestimated the 10OS\(^17\).

The consideration of EPclin score help to provide a more accurate estimation of prognosis for individual patient. In our analysis, the addition of adjuvant chemotherapy in RH-positive early breast cancer was associated with a higher benefit at 10OS for high-risk EPclin \((p=0.17)\) than low-risk EPclin \((p=0.02)\). However, this discrepancy cannot be considered as meaningful with a magnitude chemotherapy benefit at 10OS only of 0.6% in absolute difference between low and high-risk EPclin. Those data suggested a limited benefit of adjuvant chemotherapy for patient with a life expectancy around 10 years. It is consistent with the results of the phase III ASTER 70s trial that did not find a statistically
significant OS benefit with the addition of chemotherapy with ET after surgery for patients more than 70 year-old.

This study also highlighted the rate of high-risk EPclin for a population with a chemotherapy benefit less than 2% according to PREDICT. This result overturned French guidelines which considered the prescription of a genomic test for a chemotherapy benefit ranged from 2% to 5% according to PREDICT. Most of this population had less than 65 years old, with no axillary node involvement but with a high Ki67 level (> 20%) which can overlap with EPclin score. Benefit of adjuvant chemotherapy for this population is clearly uncertain and need to be discuss with the patient.

Genomic tests are indicated for primary event of breast cancer. In clinical practice, they are also used for subsequent breast cancer events which had been excluded from prospective trials. In our study, 29 women had a history of breast cancer, 23 of which had a high-risk EPclin. Probably, no genomic test needs to be prescribed in this population.

Biomarkers for adjuvant chemotherapy in early-stage breast cancer in ASCO guidelines have been recently published. Even if other genomic tests were available, OncotypeDX® had the higher quality of evidence with the strongest strength of recommendation in pre and post-menopausal patients. Endopredict test® had not been assessed in prospective, randomized trial in premenopausal women. In our population, 26% of women was premenopausal. Current data suggest that premenopausal patients with 1-3 positives nodes benefit from chemotherapy regardless of genomic assay result. For premenopausal women with lymph node negative, RH-positive, HER2-negative breast cancer, TAILLORX participants validated Oncotype DX® 21-gene recurrence score (RS) as biomarker. Patients age ≤ 50 years with an RS of 11-25 had a benefit from adjuvant chemotherapy. The absolute benefit of chemotherapy increased as the RS increased (invasive disease-free survival rate at 5 years: 92% vs 94.7% for RS 16-20 and 86.3% vs 92.1% for RS 21-25) for endocrine versus chemo-endocrine therapy.

The limitations of the present study were mainly represented by its retrospective status, the small number of patients and its estimated survival endpoints. However, it was the first study which compared the estimated survival by PREDICT and EndoPredict® results.

We are looking forward the results of two prospective, randomized trials (UNIRAD and RESCUE) which are currently accruing to evaluate EPclin prognostic and predictive efficacy.

**CONCLUSION**

EndoPredict® test well categorized patients in low and high-risk EPclin when the estimated chemotherapy benefit is ranged from 1% to 5% at 10OS. Using PREDICT survival estimation, EPclin seemed to be a predictive factor of adjuvant chemotherapy at 10OS. However, the clinical significance is still unclear with an absolute difference benefit of 0.6% between low and high-EPclin. Results of prospective, randomized trials are pending.


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**Competing Interests**
The authors have no relevant financial or non-financial interests to disclose.

**Author Contributions**
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Marc Pujalte Martin, Juliette Haudebourg, Jocelyn Gal and Renaud Schiappa. The first draft of the manuscript was written by Marc Pujalte Martin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
Data Availability

The datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics approval

This is an observational study. No ethical approval is required.

Consent to participate

Informed consent was obtained from all individual participants included in the study. For more information, please refer to the health-data-hub website, No F20220215101952.
Figure 1

Scatter plot of the estimated absolute chemotherapy treatment benefit at 10OS with Predict tool® according to EPclin. Low-risk EPclin (blue dots); high-risk EPclin (orange dots).
Figure 2

The estimated 10OS using PREDICT for high-risk EPclin compared with low-risk EPclin according to adjuvant treatment combination. (N=249)

ET : Adjuvant endocrine treatment ET + ACT : Adjuvant endocrine and chemotherapy treatment
Figure 3

Box-plot of estimated adjuvant chemotherapy benefit at 10OS using PREDICT according to high and low-risk EPclin (N = 249) The horizontal line within the box plot represents the median, the top and the bottom of each box indicate the interquartile range. Outliers are plotted separately (colorful circles)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf