Proliferative Score in Predicting Recurrence Risk of Breast cancer

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ABSTRACT

Background: Oncotype DX (ODX) is a validated clinical genomic tool that needs to be efficiently utilized especially in areas of limited resources. Proliferative genes weigh heavily in calculating Recurrence Score (RS). Ki67 is a nuclear protein highly expressed in the S phase and not in G0 phase. Assessment of tumor proliferative index by Ki67 immunohistochemistry and standard pathological grade may represent a relatively inexpensive screening approach to identify patients with a low risk of recurrence.

Methods: We retrospectively studied 205 patients with lymph node negative, hormone receptor (HR) positive, HER2 negative status (ODX candidates) treated at our community oncology practice. Proliferation index was calculated by combining tumor grade, mitotic score and Ki67 (on a scale of 1-3). Freedom from disease progression (FDP) was calculated from date of surgery to date of progression or last follow-up (FFP). Overall Survival was calculated from date of surgery to date of death or last follow-up (OS) and progression free survival was calculated from date of surgery to date of progression or death whichever came first or last follow-up (PFS). Fisher’s exact test was used to test the association of baseline characteristics with Ki67 and Mitotic index.

RESULTS

We retrospectively studied 205 patients between Jan. 1989 – Oct. 2015. Median age 64 (30 – 91) with node negative, hormone receptor (HR) positive, and HER2 negative status (Oncotype DX candidates – ODX) diagnosed and treated at our community Oncology practice. Median time to follow-up was 8.9 (0.03, 26.8) Years. We devised a Proliferation score (Prs) which was calculated by combining tumor grade, mitotic score and Ki67 (on a scale of 1-3). Prs had 96% sensitivity and a 5% specificity compared to ODX (p<0.001) [Table 2]. The Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of Prs was 99% and 95% respectively. The Area under the ROC curve for Prs was 0.83 (0.81, 0.85) [Table 4]. The Proliferation score was a significant predictor of time to progression (p=0.014) [Table 3]. The Minimum possible score of 3 and maximum score of 9 [Table 3]. Freedom from disease progression (FDP) was calculated from date of surgery to date of progression or last follow-up (FFP). Overall Survival was calculated from date of surgery to date of death or last follow-up (OS) and progression free survival was calculated from date of surgery to date of progression or death whichever came first or last follow-up (PFS). Fisher’s exact test was used to test the association of baseline characteristics with Ki67 and Mitotic index. Log-rank test was used for testing the association of proliferative score, Ki67, Mitotic score with FFP, OS and PFS. Cox proportional model was used to test the association adjusted by tumor grade.

RESULTS

There was significant association of Proliferation score (Prs) and FFP (p=0.014) [Table 2]. Patients with Proliferation Score 3 had 96%±2 FFP at 10 year past surgery compared 75%±1 for patients with Prs<3. Ki67 was significantly associated with tumor grade (p<0.001), ODX (p=0.032) and mitotic index (p<0.001) but not associated with age nor T stage. Ki67 was significantly associated with FFS (p=0.001), but no more significant after adjusted by tumor grade [Table 2]. Ninety percent of low/middle Ki67 (20%) patients did not receive chemotherapy.

METHODS

Association of Proliferation Score with Time to Progression for Breast Cancer Patients (n=190) [figure 1]

<table>
<thead>
<tr>
<th>Table 3: Pathological Proliferation Score</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67</td>
<td>&gt;10%</td>
<td>10-20%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Mitotic Index</td>
<td>1 (Low)</td>
<td>2 (Intermediate)</td>
<td>3 (High)</td>
</tr>
<tr>
<td>Tumor Grade</td>
<td>1 (Low)</td>
<td>2 (Intermediate)</td>
<td>3 (High)</td>
</tr>
</tbody>
</table>

**RESULTS**

Low Ki67 by itself or when combined with pathological data is predictive of excellent outcomes and genomic testing may unlikely re-categorize such patients. We devised a Proliferation score (Prs) which was calculated by combining tumor grade, mitotic score and Ki67 (on a scale of 1-3). There was significant association of proliferation score and FFP (p=0.014) at 5 and 10 years.

The limitations of discrepancies with lack of standardization of Ki67 staining(?) and retrospective nature of the study while important should be tested in an expanded and prospective setting.

CONCLUSIONS