The effect of background parenchymal enhancement on the predictive performance of functional tumor volume measured in MRI


1-SPY 2 TRIAL

I-SPY 2 TRIAL: A multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents as neoadjuvant therapy for high-risk breast cancer

Inclusion criteria: Tumor Size ≥ 2.5 cm; hormone-receptor (HR)+/HER2-; MammaPrint (MP) high-risk, HR-HER2- or HR+ HER2+

Primary Endpoint: Pathologic complete response (pCR)

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HR and HER2 status and MP

Regimens may leave the trial for one of four reasons: Futility (≥ 10% probability of success); Maximum sample size accrual (with probability of success ≥ 10% and ≥ 85%); Graduation (90% probability of success); or as recommended by the independent DSMB

To date: 11 experimental regimens have been evaluated for efficacy

High BPE effect on FTV calculation

- High BPE may cause inaccurate calculation of FTV
- This effect can adversely affect the predictive performance of FTV
- The change of BPE may indicate treatment response

Effect on the predictive performance

- By removing subjects with high BPE, the predictive performance of FTV was improved
- Most improvement was observed in HER2+ cancer subtype, especially HR-HER2+

CONCLUSIONS

- Our retrospective study showed adverse effect of background parenchymal enhancement on the functional tumor volume calculation and its prediction of pathologic complete response
- This effect may be adjusted by re-calculating functional tumor volume using a different signal-enhancement ratio threshold
- In future study, we will test the predictive performance of re-calculated functional tumor volume with sub-type-specific enhancement thresholds in I-SPY 2 cohort

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Strong background parenchymal enhancement (BPE) may adversely affect the predictive performance of functional tumor volume (FTV) for pathologic outcomes after neoadjuvant chemotherapy (NAC).

Purpose: This retrospective study

1. investigated the adverse effect of BPE on the predictive performance of FTV

2. proposed a potential solution to offset the effect.

Methods

All I-SPY 2 participants had series of MRI at T0 (pre-NAC), T1 (after 3 weeks of NAC), T2 (inter-regimen), and T3 (pre-surgery).

BPE was calculated as the mean enhancement compared to pre-treatment in the contralateral breast on DCE-MRI.

FTV was calculated by summing the voxels exceeding enhancement thresholds on DCE-MRI.

Statistics: The area under the ROC curve (AUC) was used to evaluate the predictive performance of FTV variables with and without high BPE subjects.

Potential solution

- Exclude gradual wash-out (FTV) in FTV calculation

- AUCs of FTV calculated with SER>0.9 were improved in HER2+ subtypes

The improvement was observed in the early treatment time point (NAC).

Consistent with prior study showing the higher SER thresholds in the optimized PE/SER thresholds for HER2+ (Li et al 2016)

Comparison of FTV vs. T0 at T1

Figure 4: Plots of AUCs of FTV changes to the prediction of pCR in 6 treatment regimens (T1 vs. T0). FTV calculated with SER>0.9 were improved in HER2+ tumors. The improvement was significant in HER2+/HR- and HER2+/HR+ tumors.

Figure 5: Plots of AUCs of predicting pCR in the early treatment time point (T1 vs. T0). FTV calculated with SER>0.9 were improved in HER2+/HR- and HER2+/HR+ tumors.

Table 1. Number of subjects and pCR rates in all and subset with no high BPE

<table>
<thead>
<tr>
<th>T0</th>
<th>Full</th>
<th>957 (72)</th>
<th>1063 (82)</th>
<th>625 (50)</th>
<th>293 (22)</th>
<th>449 (33)</th>
<th>411 (31)</th>
<th>293 (22)</th>
<th>41 (31)</th>
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<tbody>
<tr>
<td>HR/HER2</td>
<td>107 (33)</td>
<td>210 (63)</td>
<td>251 (61)</td>
<td>251 (61)</td>
<td>221 (61)</td>
<td>221 (61)</td>
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<tr>
<td>HER2/+</td>
<td>107 (33)</td>
<td>210 (63)</td>
<td>251 (61)</td>
<td>251 (61)</td>
<td>221 (61)</td>
<td>221 (61)</td>
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<tr>
<td>HR+HER2</td>
<td>107 (33)</td>
<td>210 (63)</td>
<td>251 (61)</td>
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<td>221 (61)</td>
<td>221 (61)</td>
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<tr>
<td>HR/HER2</td>
<td>57 (36)</td>
<td>30 (36)</td>
<td>57 (36)</td>
<td>57 (36)</td>
<td>47 (36)</td>
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<tr>
<td>HER2/+</td>
<td>57 (36)</td>
<td>30 (36)</td>
<td>57 (36)</td>
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<tr>
<td>HR/HER2</td>
<td>233 (60)</td>
<td>174 (60)</td>
<td>218 (60)</td>
<td>218 (60)</td>
<td>140 (60)</td>
<td>140 (60)</td>
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<tr>
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<td>140 (60)</td>
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</table>

Table 2. BPE cutoffs to define subsets with high BPE removed

| T0 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 | T13 | T14 | T15 | T16 | T17 | T18 | T19 | T20 | T21 | T22 | T23 | T24 |

- High BPE may cause inaccurate calculation of FTV

- This effect can adversely affect the predictive performance of FTV

- The change of BPE may indicate treatment response

Conclusions

- Strong background parenchymal enhancement (BPE) may adversely affect the predictive performance of functional tumor volume (FTV) for pathologic outcomes after neoadjuvant chemotherapy (NAC).

- High BPE may cause inaccurate calculation of FTV.

- This effect can adversely affect the predictive performance of FTV.

- The change of BPE may indicate treatment response.

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