Association of a 40-gene expression profile (40-GEP) with risk of metastatic disease progression of cutaneous squamous cell carcinoma (cSCC) and benefit of adjuvant radiation therapy (ART)

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Background

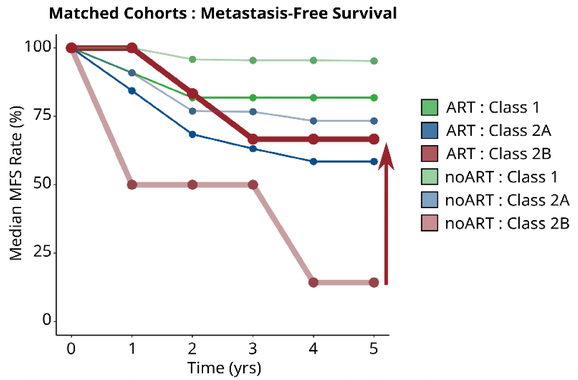
- Criteria for recommendation of adjuvant radiation therapy (ART) for cutaneous squamous cell carcinoma (cSCC) is based on a wide range of high-risk clinicopathologic features that have not been consistently demonstrated to predict benefit from ART. This has led to a broad scope of patients receiving treatment, with only a subset appearing to benefit.[2-5]
- The 40-gene expression profile (40-GEP) test is a prognostic tool which classifies patients with a primary cSCC who have one or more clinicopathologic risk factors into low (Class 1), moderate (Class 2A), and high (Class 2B) risk of regional, nodal, or distant metastasis.[6]
- Published validation studies indicate that the 40-GEP test provides additive prognostic value to current risk assessment methods,[6] and may positively influence treatment decisions for high-risk cSCC patients.[7,8]

Methods

- Initial eligible patients consisted of a merge of two validation cohorts for the 40-GEP test for which patients were confirmed as eligible for testing and had a successful 40-GEP test result (n=954). After patient exclusions specific to this study were applied, all 920 qualifying patients were matched on clinical risk factors, stratified by ART status. Random sampling (x10,000) of ART status pairs and bootstrapping were used to avoid dropping any qualified patients and allow results to be generalizable to the cSCC high-risk population. Each sampled and resampled cohort was analyzed using survival methods and stratified by GEP result and ART status.

Results

Figure 1. Matched cohort analysis shows benefit of ART for patients with a Class 2B cSCC for 5-year MFS



- Median MFS for the six 40-GEP x ART status groups from x10,000 sampled cohorts. Red arrow indicates the ~50% increase in 5-year MFS specifically for Class 2B patients that received ART.

Clinical Issue and Objective

Use of ART in cSCC has been shown to benefit some patients; but use of clinicopathologic factors to identify patients who are likely to benefit from those who may not is a major clinical challenge.

The objective of this study was to determine whether the biology 40-GEP test could identify high-risk cSCC patients who achieve benefit from ART in controlling metastatic disease progression from those who may not.

Table 1. Class 2B result is the only factor in the study that identifies patients that will benefit from ART, in contrast to clinicopathologic risk factors or risk assessment systems

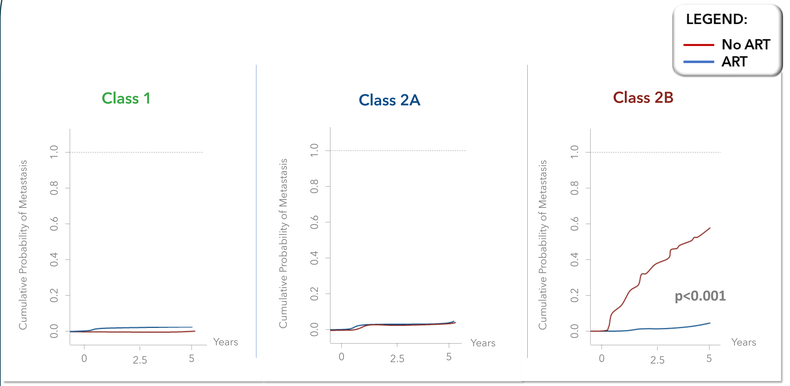
	Level	Median Difference Time to Event with ART (yrs)	D-observed (p-value*)
40-GEP	Class 1, 2A, **2B**	-1.80, -1.62, **+5.59**	>0.05, >0.05, **<0.01**
Risk factor			
NCCN location	L, M, H	-2.98, -3.41, -1.37	>0.05 for all
Immunocompromised	Yes, No	-0.78, -2.09	>0.05 for all
Differentiation status	Well or moderate, Poor	-0.62, -0.98	>0.05 for all
Invasion into fat	yes, no	-1.23, -0.75	>0.05 for all
Tumor diameter	<2cm, ≥ 2cm	-2.01, -1.51	>0.05 for all
PNI	< 0.1mm, ≥ 0.1mm	-2.3, -1.4	>0.05 for all
Tumor thickness	< 6cm, ≥ 6cm	-1.10, -1.76	>0.05 for all
Surgery type	Mohs, WLE, other	-11.8, -0.02, -1.07	>0.05 for all
Risk assessment method			
NCCN risk category	High, Very High	-1.49, -0.85	>0.05 for all
BWH T-stage	Low (T1/T2a), High (T2b/T3)	-0.77, -0.89	>0.05 for all
AJCC8 T-stage	Low (T1/T2), High (T3/T4)	-1.80, -0.40	>0.05 for all

- Experimental analyses tested whether any risk assessment system or any the clinicopathologic risk factors used for matching, when combined with ART status, could themselves be used to identify patients that would benefit from ART treatment; none were able to identify a patient group that would potentially benefit from ART treatment. Only 40-GEP Class 2B patients were identified as benefiting from ART treatment.

Conclusions

- The 40-GEP identified patients who benefitted most from ART with improved metastasis-free survival and delay or abrogation of nodal or distant metastasis.
- The 40-GEP test was also able to identify those patients who were less likely to show significant benefit from ART in controlling metastatic disease progression.
- The 40-GEP test can identify patients who would most likely benefit from ART as a reduction in metastatic disease progression.

Figure 2. Class 2B patients receiving ART show significant reduction in cumulative probability of metastasis



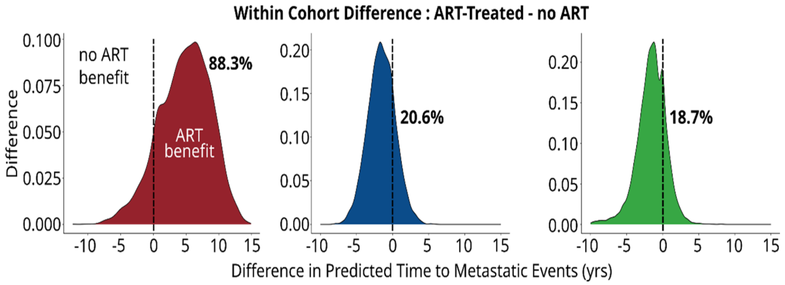
No significant impact of ART in cohort as a whole or within Class 1

No significant impact of ART in cohort as a whole or within Class 2A

ART treated Class 2B patients see significant reduction in metastasis*

Cumulative distribution plots (Kolmogorov-Smirnov 2-sample test), show the underlying function of disease progression. Class 1 and Class 2A, ART- and non-ART-treated patient cohorts accumulated metastatic events according to a sigmoidal function, in sharp contrast, non-ART-treated Class 2B patient cohorts showed exponential accumulation of events

Figure 3. Within cohort differences in predicted metastasis progression. Eighty-eight percent (88%) of Class 2B patients receive a benefit from ART



- Within-cohort differences in predicted disease progression. Percentage of within-cohort delay in disease progression (ART benefit) is indicated. eCDF = Empirical Cumulative Density Function; *p<0.01; not significant for Class 1 and Class 2A.

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Disclosures

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