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Survivin Expression and Impact On Head And Neck Cancer Outcomes

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Abstract

Introduction: Survivin is an inhibitor of apoptosis that is proposed as a target for anti-cancer therapy because of its high expression in cancer cells. It also has potential as a prognostic and predictive biomarker of response to radiation and system therapies. We report its expression in head and neck squamous cell carcinoma (HNSCC) and correlation with treatment response and survival.

Methods: We measured survivin protein expression in tumor specimens from 96 patients with HNSCC treated at Fox Chase Cancer Center, of whom 21 were p16+. Quantitative automated immunofluorescence was employed to score nuclear and cytoplasmic survivin in 5 tissue microarrays (TMAs) consisting of 316 H&N tumor cores and 107 control tissue cores. Survivin levels were then correlated to therapy response and survival outcomes.

Results: Using the median score as the cutoff, overall survival (OS) was significantly shorter for the group expressing higher survivin in nuclear (p=0.013), cytoplasmic (p=0.018) and total compartments (p=0.006). No correlation was seen between survivin expression and patient sex or grade of tumor, T or N stage, or p16 status. Survivin expression in metastases did not significantly differ from primary tumors. Levels of p53 expression were available for all patients and showed a significant positive correlation with higher survivin expression in the cytoplasm (p=0.0264) and total compartments (p=0.0264), but not in the nucleus (p=0.0729).

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Conclusions: Survivin expression above the median is associated with shorter overall survival in HNSCC, including for patients treated with chemotherapy or radiation. p16 expression did not correlate with survivin levels.

Introduction:

Head and neck squamous cell carcinoma (HNSCC) affects approximately 65,000 patients annually. [1, 2] Prognostic biomarkers have transformed our understanding and approach to HNSCC [3, 4]. Human Papilloma Virus (HPV)[5] DNA or RNA expression and p16 positivity[6] are associated with superior outcomes after standard therapy in oropharyngeal carcinoma. Excision repair cross-complementing group 1 (ERCC1) levels are associated with varied survival in patients treated with surgery and adjuvant radiation. [7] The Combined Positive Score scores expression of Programmed Death Ligand 1 (PD-L1) in tumor and immune cells to predict effectiveness of pembrolizumab monotherapy.[8] Yet there are no chemotherapy biomarkers which might help reduce patient toxicity and avoid futile treatment. HNSCC trials are assessing p16, *TP53* disruptive mutation, PD-L1 and others as possible predictive or prognostic biomarkers that justify treatment de-escalation or escalation (NCT01898494, NCT02734537, NCT02255097, NCT02207530). Predictive biomarkers have immediate application, however prognostic biomarkers in head and neck cancer might allow selection of patients for more intensive therapies for patients expected to have worse outcomes.

Survivin is an ideal target for therapy because it is nearly absent in normal adult tissue but highly over-expressed in cancer cells. Finding drugs that effectively target survivin has proved difficult, though newer molecules show promise. It is therefore essential to understand the prevalence and biologic impact of survivin expression in HNSCC. Survivin is associated with programmed cell death, apoptosis, and interferes with cellular proliferation, which are the intended effects of chemotherapy and radiation.[9, 10] Survivin overexpression appears to aid cancer cell survival by reducing caspase activity which leads to reduced apoptosis. [11, 12] Reducing survivin levels in cancer cells interferes with their DNA-repair ability and increases the likelihood that radiation damaged cells start the process of mitosis. [13, 14] Survivin in cancer cells is continuously synthesized and is transcriptionally de-repressed.[15] Small molecules targeting survivin such as YM155[16] and PD-1 based vaccines targeting survivin and MUC1[17] have demonstrated limited efficacy as single agents, though cancer cells exposed to YM155 appear more likely to undergo radiation induced apoptosis instead of senescence. [18]

Survivin is encoded by the *BIRC5* gene at 17q25 [19] yielding a protein with 142 amino acids with a single amino-terminal BIR1 domain and single carboxy-terminal coiled-coil domain.[10, 20] Survivin's function and impact on the cancer cell has been proposed to vary with its sub-cellular localization. [21–23] Survivin localizes with HPV in cervical cancer (with unclear clinical and biological significance); but in oropharyngeal cancer there does not appear to be a similar relationship between HPV, survival and outcomes. [24, 25] Cytoplasmic survivin shows a stronger relationship with preventing apoptosis, [26, 27] and how survivin enters the nucleus is unclear [24]. Prior studies have reported inconsistent

relationships between survivin levels in cytoplasmic or nuclear localization with survival and prognosis.

The present study sought to clarify the role of survivin in head and neck cancer using highly quantitative methods and the largest dataset to date with complete clinical annotation. Quantitative immunohistochemical staining assessment of biomarkers is an important advance with broad application to assessing tumor protein expression and prevalence of cell types.[28, 29] We employed advanced automated reading of quantitative in situ immunofluorescence to better define high vs. low expression, using a commercially available platform that results in automated and highly quantitative IHC scores, to reduce inter-observer variability and enhance reproducibility, and to address the potential role of survivin sub-cellular localization for its prognostic and predictive value in HNSCC. Our hypothesis was that survivin levels will impact cancer outcomes and response to therapy.

Materials/Methods:

Patients:

As previously described[7], surgical samples collected from 96 patients who underwent resection of HNSCC at Fox Chase Cancer Center between 1990 and 2007 were studied. Prior to surgery, patients provided IRB-approved informed consent to tissue analysis as well as review of treatment and outcomes data. Tissue microarrays (TMAs) were constructed from 316 core samples of both primary tumors and nodal metastases in duplicate; controls were included directly in the TMA blocks and underwent identical testing. Results were connected to anonymized patient information including demographics, tumor histology/grade/site, disease history and outcome, and detailed chemotherapy-radiation administration as well as p16 and p53 expression level for all specimens analyzed.

Immunohistochemistry analysis:

All samples were interrogated using the previously described methods[7] with the AQUA® platform (HistoRx, Branford, CT) yielding specific survivin expression scores in the total cell, nuclear and cytoplasmic compartments. Immunofluorescent staining with commercial survivin antibody (Novus Biologicals™ NB100-56168) was optimized for staining at dilution 1:5000 with Cy5 conjugate at a 1:200 dilution. TMAs were imaged using a computer-controlled motorized microscope to acquire high-resolution images using different filters. Survivin levels were reported for each individual cellular compartment separately, (e.g. nuclear, cytoplasmic and total) and correlated with response to radiation/chemotherapy and to overall survival. CK and DAPI antibodies were used for cytoplasmic/nuclear localization. Visual validation of each image was employed to exclude cores with <5% tumor, excess debris or poor staining.

Statistical analysis:

Values of different samples from same subject in the same compartment were averaged and average values used for analysis. Relationship of survivin expression with age was explored using scattered plot and tested using Spearman correlation. Relationships with tumor grade, stage, and metastases were explored using box plot for each category. Correlations with

grade and stage were tested using Cochran–Armitage test for trend and correlation with metastases was tested using Chi-squared test.

Overall survival was defined as the time from diagnosis to death, and disease-free survival as the time from treatment until evidence of recurrence. Survivin is a novel biomarker without defined ranges for what constitutes high or low expression. Published approaches to determine the significance of novel biomarkers include dividing patients into groups by median and quartile survivin expression levels. [30–32] Overall survival and disease-free survival by quartile and median were characterized using Kaplan-Meier curves. Log-rank test was used to compare the survival for different levels of Survivin expression. Statistical analyses were performed using Stata 12 software, (Stata Corporation, College Station, Texas)

Results:

Survivin positivity in cellular compartments

Primary tumor specimens from 96 patients were submitted to survivin immunofluorescence and AQUA analysis. Overall survivin expression score in the tumor cells measured by the AQUA platform ranged from 115–1499 in total with a median of 235. Survivin score in the nucleus ranged from 124 to 2371 with a median of 341; in the cytoplasm range was from 102 to 1283 with a median of 235.

Survivin expression and patient variables

The TMA included samples from 64 men and 32 women ranging in age from the third to ninth decade of life. Increasing age was correlated with higher survivin expression ($p=0.0042$). This was seen in both nuclear and cytoplasmic compartments as well as total cellular expression (Figure 1a). No statistically significant difference was observed between survivin expression and patient sex (Figure 1b).

Survivin expression and Tumor Grade, Stage, and Metastases:

AQUA was performed for quantitative survivin expression on paired primary tumor and metastatic-site biopsy samples obtained from 19 patients; no statistically significant differences were observed in nuclear, cytoplasmic, or total survivin expression between primary tumors and their metastases (Table S1). Further, no statistically significant correlation with survivin expression by AQUA was found with tumor grade or stage across the entire cohort of patient samples (Tables S2, S3).

Survivin correlation with p16 and p53

To evaluate survivin in context of validated biomarkers, head and neck cancer samples were further submitted to IHC staining for p16 expression. Although survivin levels were consistently numerically higher in p16-negative cases, there was no significant difference in median survivin score in the nuclear (367/319, $p=0.15$), cytoplasmic (219/189, $p=0.32$) or total compartments (242/219, $p=0.24$) by p16 status in this cohort with 21 p16-positive cases. In addition, no correlations were observed between p53 and survivin expression levels in nuclear, cytoplasmic or total compartments (Figure 2).

Overall and Disease-Free Survival:

Patient samples were divided into groups by both median and quartile of survivin expression through quantitative immunofluorescence and evaluated for disease-free (DFS) and overall survival (OS). Higher survivin expression correlated with shorter OS. Dichotomizing at the median score, the survivin-high group had significantly shorter OS, whether measured in the nuclear (p=0.013), cytoplasmic (p=0.018) or total compartments (p=0.006) (Figure 3a-c). When survivin expression was analyzed by quartiles, there was a shorter OS associated with the highest quartiles of survivin expression in the nuclear (p=0.006), cytoplasmic (p=0.022) and total (p=0.008) compartments (data not shown).

Disease-free survival (DFS) did not vary with high and low survivin expression in nuclear (p=0.075), cytoplasmic (p=0.443) or total compartments (p=0.411). When survivin expression was divided into quartiles, there was no difference in DFS with survivin expression in nuclear (p=0.092), cytoplasmic (p=0.396) or total compartments.

Survivin expression and outcomes after radiation or chemotherapy

Of the total cohort, 66 patients received neoadjuvant and post-operative radiation therapy as a component of treatment with curative intent. Among radiated patients, shorter OS was seen for patients with higher than median survivin in the cytoplasm (p=0.015) and total compartments (p=0.016); this difference was not significant for nuclear survivin (p=0.100) (Figure S1a-f). When patients were segregated by median survivin expression, there was a trend towards shorter DFS for high nuclear survivin (p=0.052), but not for cytoplasmic (p=0.167) and total compartment (p=0.180) high survivin expression.

Of the total, 17 patients received chemotherapy; nine received taxane-based regimens. Shorter OS was seen in chemotherapy-treated patients with higher than median survivin in nuclear (p=0.006), cytoplasmic (p=0.024) and total compartments (p=0.006) (Figure S1a-f). In chemotherapy patients, no significant difference in DFS was noted between the high and low survivin group in any compartment.

Discussion:

Our analysis demonstrates that survivin expression varies amongst patients with HNSCC and that higher levels of survivin are associated with inferior OS independent of p16 status, treatment modality or cellular compartment. The purpose of this study was to apply sophisticated quantitative biomarker analysis techniques to a large comprehensively annotated patient dataset in order to determine whether survivin expression impacts HNSCC patient survival. This analysis in nearly 100 HNSCC patients is the largest conducted for this protein biomarker and suggests current testing techniques using quantitative immunohistochemistry with commercially available survivin antibodies can identify head and neck cancer populations with inferior outcomes. Of note, there was no significant correlation seen between cancer outcomes and survivin expression in The Cancer Genome Atlas, though HNSCC with survivin gene alteration appear to have an inferior median disease-free survival compared to those without survivin alterations.

Prognostic biomarkers play an important role in HNSCC treatment independent of whether they also predict for response to specific therapies. Survivin did not predict for response to specific chemotherapies, radiation or surgery so currently functions as a prognostic biomarker. Prognostic biomarkers such as p16 positive HNSCC have transformed our understanding of the etiology, staging, therapeutic approach, clinical trial design and outcomes in this disease. Survivin is a similar biomarker whose increased expression appears associated with inferior survival, with the added benefit of being highly cancer cell specific and potentially druggable. In our analysis, there was no correlation of survivin seen with p16 expression or p53 mutation status suggesting that survivin is prognostic independent of these well-established biomarkers. Unlike p16 and HPV positive HNSCC where the inciting event is clear, we do not yet know what causes HNSCC survivin expression. It is unclear if survivin expression is the result of as yet unknown environmental exposure that led to carcinogenesis. We also do not know if the inciting event for survivin expression is modifiable. Survivin overexpression may identify HNSCC populations that may benefit from treatment intensification, and distinguish the minority of p16+ HNSCC that has poor outcomes even with standard therapy. Our analysis suggests that survivin identifies patients with an inferior overall survival regardless of subsequent treatment, which may allow survivin patients to be selected for therapy intensification rather than waiting for pathologic findings. Survivin levels can be determined using commercially available antibodies.

The negative impact of high survivin expression on overall survival in HNSCC is consistent in different cellular compartments, patient demographics and independent of treatments given. Our analysis is the first to identify high survivin expression in any cellular compartment (nucleus, cytoplasm or total) as being associated with inferior overall survival. We did not identify any difference in survivin expression by age or gender, which suggests that our findings were not an artefact of p16 status.

Survivin expression may thus represent a common final pathway in HNSCC patients regardless of whether they had previously been exposed to HPV. A prior analysis of 40 HNSCC patients identified a longer overall survival with higher survivin levels and also demonstrated an association with better response to radiotherapy with higher survivin levels[33]; our analysis of 66 radiated patients found that higher survivin levels were associated with an inferior overall survival. Survivin has been implicated as mechanism by which cancer cells may evade paclitaxel-induced apoptosis[34, 35]. In our analysis survivin did appear to predict for a reduced response to taxane-based chemotherapy without reaching statistical significance, but there was still an association between inferior survival and higher survivin levels in patients who received chemotherapy at any time. The difference between our analysis and prior publications indicates the critical importance of a superior technical platform that can differentiate between nuclear and cytoplasmic survivin vs its total cellular expression. In addition, our sample size was significantly larger, allowing us to identify statistically significant associations where a smaller analysis may not have had sufficient power to do so.

There are some limitations in our study design related to the retrospective nature of our analysis. The strengths of our study are in highly quantitative, automated

immunohistochemical process of analyzing survivin expression which minimizes inter-observer variation and improves reproducibility. Our study also adds upon prior work by being able to determine survivin expression in nuclear and cytoplasmic cellular compartments, where it plays a unique role in each. This clearly remains an area where further study is warranted

In the future, high survivin expressing HNSCC patients may thus serve as an ideal population for testing newer therapies; building on the older targeted YM155 experience [16] and the newer survivin-specific vaccine approaches.[17] Survivin also appears to safeguard chromosomal stability independent from p53. [36] This suggests that patients expressing high survivin levels may be candidates for higher dose cisplatin to result in the same amount of DNA-damage. This may augment clinical factors used to determine whether high-dose or low dose cisplatin will result in superior patient outcomes.[37] Other options include evaluating survivin's role in predicting for response to specific chemotherapies in larger patient subsets especially in those receiving taxanes or DNA-damaging agents. Additional studies to evaluate the mechanisms of differential survivin expression as well as inferior outcomes in HNSCC will be crucial to refining its role as a biomarker. The relatively simple method of determining survivin expression by IHC suggests that interventional clinical trials with survival outcomes could retrospectively compare outcomes for HNSCC with high and low survivin expression.

In conclusion, our retrospective identification of higher survivin expression being associated with inferior overall survival suggests it is a prognostic biomarker for inferior overall survival across HNSCC regardless of HPV association or anatomic subsite. This negative association persists regardless of therapies given and independent of age or gender. Survivin may thus have utility in identifying populations to be enrolled on to intensification or de-intensification studies divided by high or low survivin status. Similarly, ensuring an balanced spread of survivin high and low expression in patients on clinical trials may reduce potential confounding of the intervention in question. Survivin thus is a promising biomarker in HNSCC with a potential role to better understand the biology of squamous cell cancer and to identify populations with inferior outcomes with current therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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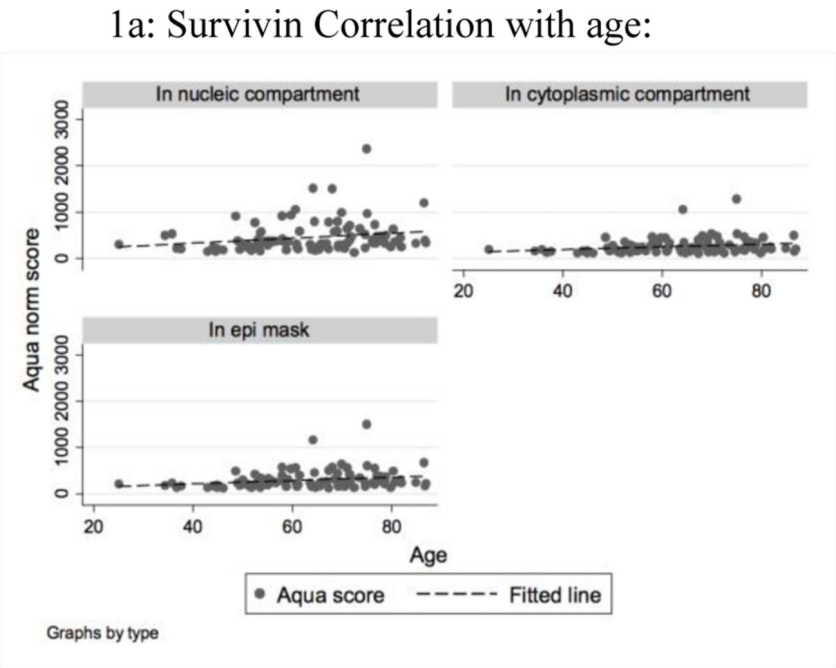
Research Highlights:

Survivin is a protein biomarker highly expressed head and neck cancer cells.

High nuclear or cytoplasmic survivin expression impacts patient cancer outcomes.

High head and neck cancer cell survivin expression is a negative prognostic marker.

A new class of drugs targeting survivin is based on its high expression in cancer.



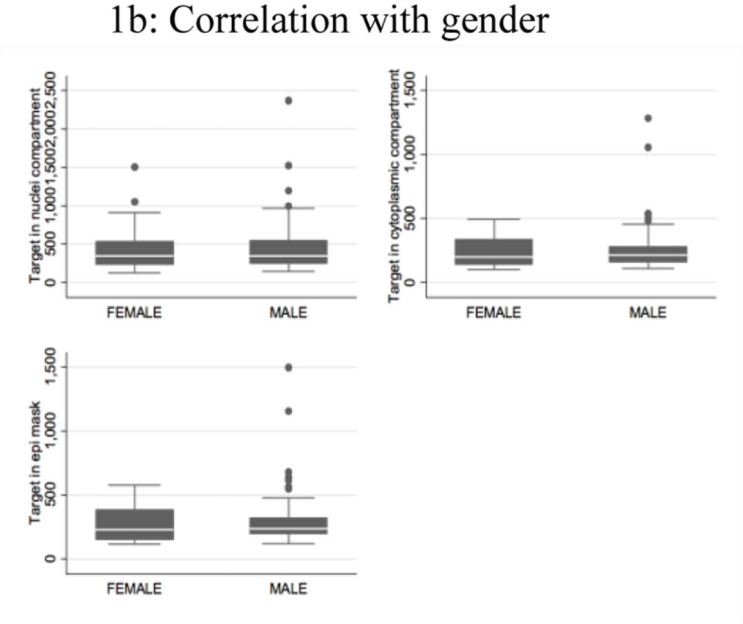


Figure 1:

TMA-AQUA analysis of 100 patient HNSCC biopsies stratified by age (a) or gender (b). Increasing immunofluorescent intensity of Survivin was found to be highly correlated to increasing patient age in the nuclear (Prob > |t| = 0.0042), cytoplasmic (Prob > |t| = 0.0092), and total cellular compartments (Prob > |t| = 0.0092); however, no association was found with patient gender across cellular compartments ($p > 0.4$).

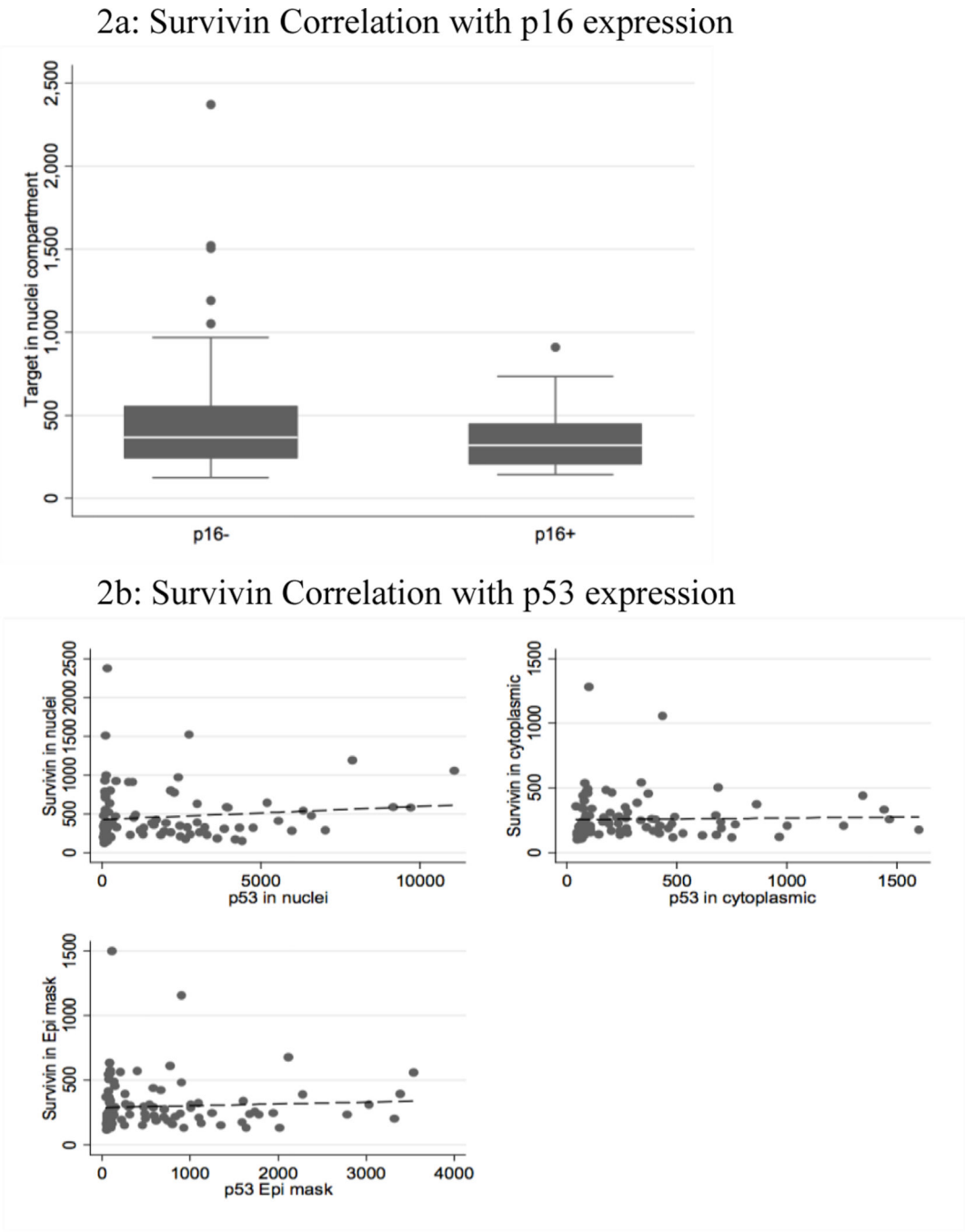
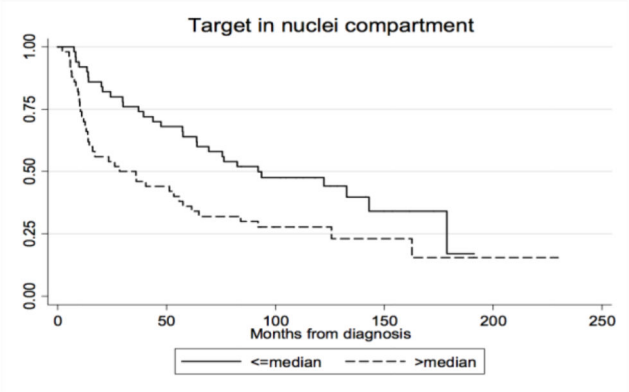


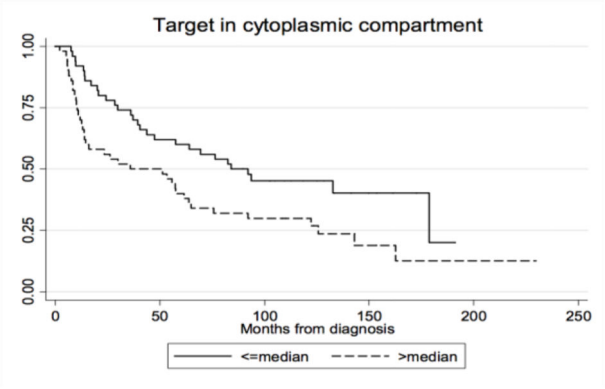
Figure 2:

Expression of Survivin when compared to biomarkers p16 and p53. No correlation was found between either p16 (a) or p53 (b) across cellular compartments.

3a: Nuclear Survivin Correlation with OS



3b: Cytoplasmic Survivin Correlation with OS



3c: Total Cellular Survivin Correlation with OS

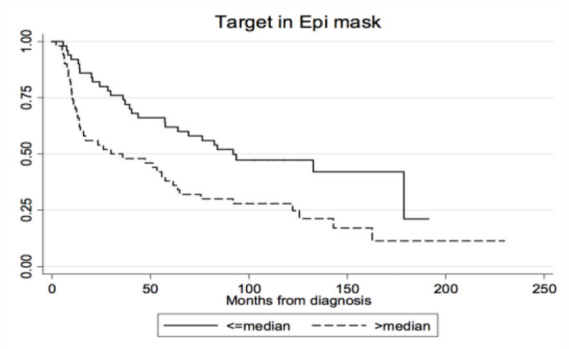


Figure 3:

Overall Survival is inversely correlated to Survivin expression across nuclear (Figure 3a, P>|z| = 0.013, 95% C.I. 1.136043 – 2.973603), cytoplasmic (Figure 3b, P>|z| = 0.018, 95% C.I. 1.102131 – 2.888597), and total cellular compartments (Figure 3c, P>|z| = 0.006, 95% C.I. 1.222716 – 3.22467).