Clinical Oral Investigations (2019) 23:361–367
https://doi.org/10.1007/s00784-018-2444-8

ORIGINAL ARTICLE

Survivin expression in head and neck squamous cell carcinomas is frequent and correlates with clinical parameters and treatment outcomes

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Received: 16 August 2017 / Accepted: 12 April 2018 / Published online: 18 April 2018

Abstract

Objectives Strong expression of survivin is associated with worse survival in many different tumours, and in cell culture, a correlation between radiation resistance and survivin expression can be seen. The potential of survivin expression as a prognostic/predictive marker or therapeutic target has not been examined in head and neck squamous cell carcinomas (HNSCC) yet.

Material and methods Retrospective study of 452 tissue samples and clinical data from patients with squamous cell carcinomas of the larynx/hypopharynx (LSCC), oral cavity (OSCC) and oropharynx (OPSCC) treated in the University Medical Centre Hamburg-Eppendorf between 2002 and 2006. The expression patterns were detected by tissue microarray technique and correlated with clinical parameters (sex, age, tumour location, TNM 7th edition, grading, recurrence-free and overall survival).

Results 222 OSCC, 126 OPSCC and 105 LSCC tumours of 118 females and 335 males with a mean follow-up of 41.3 months were examined. Survivin expression correlates with pN, cM, pT and overall survival.

Conclusion and clinical relevance The potential of survivin as a prognostic/predictive marker is very high. The findings have to be confirmed in a larger cohort of HNSCC esp. in those tumours treated primarily with radio/radiochemotherapy.

Keywords Survivin · Prognosis · Head and neck squamous cell carcinoma (HNSCC)

Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers, with a global incidence of 500,000 cases per year, and is the sixth most common malignant tumour worldwide [1]. Despite significant advancements in diagnosis, disease management and novel treatment strategies to improve quality of life (QoL) in patients, the 5-year survival rate for HNSCC has not improved appreciably over the last decade [2–7]. The treatment of HNSCC comprises multiple-modality therapy with cytostatic drugs and radiotherapy, and is often combined with sophisticated surgery. However, radio- and/or chemotherapy resistance and tumour recurrences are key clinical issues in the management of HNSCC [6]. Therefore, identifying predictive elements of treatment response is critically necessary. Intriguingly, survivin is expressed in embryonic as well as foetal tissues, but is undetectable in normal adult tissues [8]. Previous studies have indicated survivin expression and its evolving functional complexity in head and neck cancer carcinogenesis [9, 10]. Survivin overexpression has been noted in a wide range of

No author has a financial or proprietary interest in any material or method mentioned.

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clinical cancers including bladder [11], breast [12], colorectal [13], oesophageal [14], gastric [15], lung [16], nasopharyngeal [17], pancreatic [18], prostatic [19], ovarian [20], renal [21], skin [22] and haematological cancers [23]. The induction of a natural antisense of survivin, effector cell protease receptor-1 (EPR-1), in a human colon cancer cell line resulted in the downregulation of survivin expression, with a similar decrease in cell proliferation, an increase in apoptosis and an increase in the sensitivity to anticancer agents [24]. Higher expression of survivin as a critical factor for radioresistance in HNSCC cell lines has also been demonstrated [25]. Thus, for HNSCC, the identification of biological prognostic markers indicating an increased risk of treatment failure could prove beneficial in the treatment modalities as well as the intensity of post-therapeutic follow-up [9].

Survivin, also known as baculoviral inhibitor of apoptosis protein repeat-containing 5 (BIRC5) and a member of the inhibitor of apoptosis protein (IAP) family, is a 16.5 kDa protein with a single baculovirus IAP repeat (BIR) and no really interesting new gene (RING) finger domain [5, 26]. It is the smallest member of the IAP family that inhibits caspases and blocks cell death, is highly expressed in most cancers and is associated with a poor clinical outcome. At the molecular level, survivin could be a multifunctional suitable protein for targeted therapy, not only playing a vital role in cell division but also inhibiting apoptosis (antiapoptotic function) and enhancing angiogenesis [1, 27, 28].

The prognostic value of survivin for many human cancers is apparent: it is correlated with an unfavourable clinical outcome. These findings suggest that survivin expression has the potential for use as a predictive biomarker in identifying cancers [29]. The high expression of survivin in cancer cells, with little expression in most normal tissues, makes survivin a potential anticancer molecular therapeutic target with multiple anticancer activities. The purpose of this study was to show the expression of survivin in a large cohort of HNSCC. We hypothesise that the expression of survivin has a high potential as prognostic and /or predictive marker in the treatment of HNSCC.

The specific aims of the study were (1) to detect the expression of survivin in HNSCC and (2) to correlate the findings with clinical parameters (age, sex, TNM, grading and tumour location) and survival data (RFS/OS).

Material and methods

Study design and samples

To address the research purpose, we designed a retrospective analyses of all patients treated with an HNSCC in the University Medical Centre Hamburg, Department for Head and Neck Surgery and Oncology from the years 2002 to 2006. Inclusion criteria were a primary tumour treatment either by surgery or radio (chemo) therapy alone or treatment in a combined surgical and risk based adjuvant setting. Patients not being suitable for therapy or presenting with recurrent disease were not included in the study.

The study was approved through the local ethics commission.

Variables

Cytoplasmic staining was evaluated by staining intensity (0, 1+, 2+, 3+) and the fraction of positive tumour cells was scored for each tissue spot.

An overall score was derived from these two parameters. Negative scores had a staining intensity of 0 and 1+ in ≤ 10% of tumour cells; weak scores had a staining intensity of 1+ in > 10% and ≤ 70% of tumour cells or a staining intensity of 2+ in ≤ 30% of tumour cells; moderate scores had a staining intensity of 1+ in > 70% of tumour cells, staining intensity of 2+ in > 30% and ≤ 70% of tumour cells or a staining intensity of 3+ in ≤ 30% of tumour cells; and strong scores had a staining intensity of 2+ in > 70% of tumour cells or a staining intensity of 3+ in > 30% of tumour cells. Examples of IHC stainings can be seen in Fig. 1. Additionally, for dichotomic analysis, all negative and weak cases were grouped as low-expressing tumours, whereas moderate and strong cases were grouped as high-expressing tumours.

Clinical parameters

As predictor variable, the TNM Classification of Malignant Tumours 7th edition UICC was used. We used the pathological staging (pT/pN/pM) for surgically resected tumours and the clinical staging (cT/cN/cM) for those treated primarily by R(C)T.

Staging was obtained by neck ultrasound, neck MRI, chest, abdominal CT and panendoscopy. Survival data was recorded as overall survival (OS) and recurrence-free survival (RFS). Recurrence-free survival was defined as time till tumour relapse after initial therapy (operation, radio- and/or chemotherapy) later than 3 months after end of therapy. Overall survival was defined as time till death or end of follow-up. Patients were censored for RFS without evidence of tumour recurrence at last follow-up or censored for OS at last documented follow-up. Tumour localisations were described according to the typical HNSCC subtypes oral cavity, oropharynx and larynx.

Patient data

The study retrospectively evaluated 453 cases of HNSCC including 222 oral (49%), 126 pharyngeal (27.8%) and 105 laryngeal (23.2%) tumours. The tumours were obtained from 118 females (26.1%) and 335 males (73.9%). The cohort consisted of 103 pT1 (23.1%), 133 pT2 (29.9%), 79 pT3

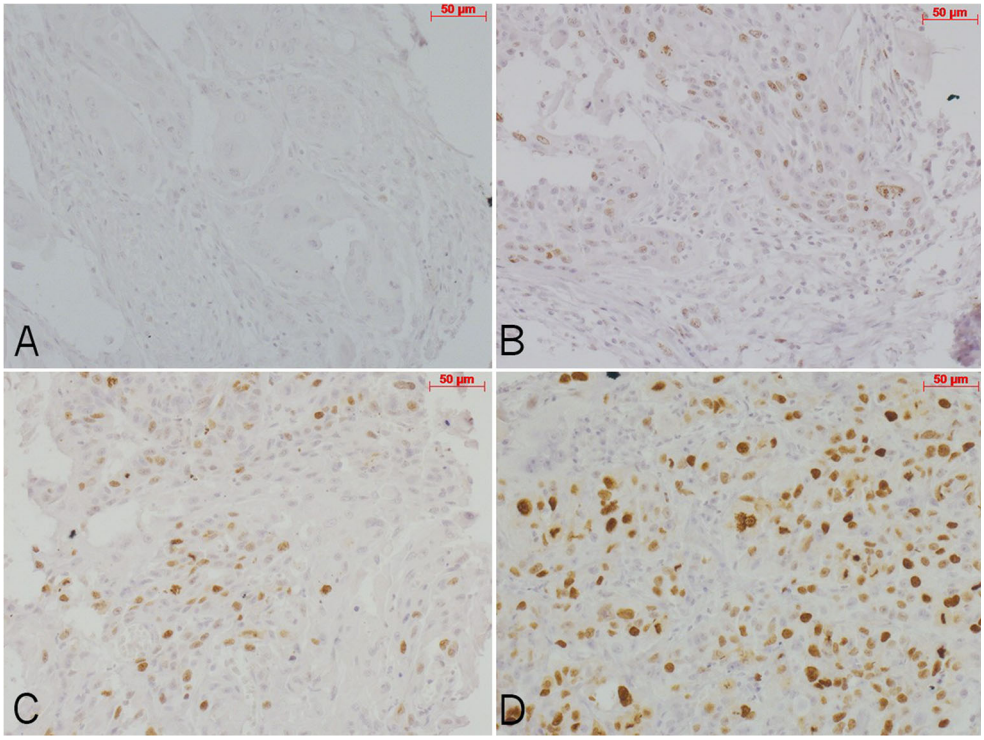

Fig. 1 Immunohistochemical (IHC) staining of head and neck squamous cell carcinoma (HNSCC) tissue. **a** Sample with negative staining intensity for survivin (score 0). **b** Sample with a weak staining intensity for survivin (score 1). **c** Sample with a medium staining for survivin (score 2). **d** Sample with a strong staining for survivin (score 3)

(17.8%) and 130 pT4 tumours (29.2%). Of these cases, 219 were in pN 0-stage (49.2%), 68 were pN1 (15.3%), 134 were pN2 (30.1%) and 24 were pN3 (5.6%). Thirty cases showed distant metastatic disease (pM1/cM1; 6.8%), whereas all other patients were defined as cM0 status. Follow-up data were available for 441 patients, ranging from 1 to 306 months (mean = 41.3 months).

Detailed clinical and pathological data is shown in Table 1 in the Results section.

Tissue microarray construction

All samples were stored and analysed in the Department of Pathology in the University Medical Centre. Tissue samples were fixed in buffered 4% formalin, embedded in paraffin and used for tissue microarray (TMA) construction. Haematoxylin-eosin stained sections were made from each selected primary tumour block to define the representative tumour region. One tissue cylinder (0.6 mm in diameter) was then punched from each tumour of that region of the block, using of a homemade semi-automated tissue arrayer [30]. The control samples included larynx ($n = 11$), hypopharynx ($n = 3$), tonsil ($n = 3$), tongue ($n = 2$), epiglottis ($n = 1$), lymph node ($n = 4$), lung ($n = 4$), heart muscle ($n = 4$), endometrium ($n = 2$), skin ($n = 2$), skeletal muscle ($n = 2$), colon mucosa ($n = 2$), stomach ($n = 2$), prostate ($n = 2$), liver ($n = 2$) and kidney ($n = 2$). Three micrometre sections were made using the Paraffin Sectioning Aid System (Instrumentics, Hackensack, NJ) and used for immunohistochemical (IHC) staining.

Immunohistochemistry

Freshly cut 3-µm TMA sections were analysed on the same day in a single experiment. Survivin (Abcam, rabbit monoclonal, 1:900) after preoxidase blocking with H_2O_2 (DAKO S2023) for 10 min. High-temperature pretreatment of slides was carried out in an autoclave with a citrate buffer at pH 7.8 for 5 min. The Envision™ system (DAKO 5007) was used to visualise the IHC staining.

Statistical analysis

For the statistical analysis, JMP 11.0 software (SAS institute Inc., Cary, NC, USA) was used. All p values were 2-sided and p values < 0.05 were considered significant. To study the relationship between survivin expression and clinicopathological parameters, a contingency table analysis and Chi-square test (likelihood) was used. Analysis on recurrence-free and overall survival rates were evaluated by using the Kaplan–Meier method and compared via log-rank test.

Results

Survivin expression in HNSCC

Evaluation of 453 cases of primary HNSCC (oral cavity (OSCC), oropharynx (OPCC) and larynx (LSCC)) revealed that 299 tissue samples were interpretable for IHC

Table 1 Clinical and pathologic characteristics of 453 patients

Characteristics	Study cohort on TMA number of patients (%)
Localization	
Oral cavity	222 (49)
Hypo-/oropharynx	126 (27.8)
Larynx	105 (23.2)
Follow-up (months)	
(Recurrence-free survival)	
Median	23.92
Mean	34.64
(Overall survival)	
Median	29.04
Mean	41.28
Age (years)	
< 40	18 (3.98)
40–49	65 (14.48)
50–59	158 (34.95)
60–69	134 (29.64)
> 70	77 (17.03)
pT category (WHO 2009)	
pT1	103 (23.14)
pT2	133 (29.88)
pT3	79 (17.75)
pT4	130 (29.21)
pN category (WHO 2009)	
pN0	219 (59.21)
pN1	68 (15.28)
pN2	134 (30.11)
pN3	24 (5.39)
cM category	
cM0	409 (93.16)
cM1	30 (6.83)
Grade	
1	31 (6.99)
2	318 (71.78)
3	92 (20.76)
4	2 (0.45)
UICC category	
I	73 (16.7)
II	72 (16.4)
III	83 (18.9)
IV	209 (47.8)

Numbers do not add up to 452 in the different categories because of cases with lack of data

cytoplasmic and/or membranous survivin expression (66%). The remaining 154 samples were noninformative. The decrease in sample size was due to absence of tissue on the TMA or a lack of unequivocal tumour cells in the arrayed samples. Table 1 represents an overview of clinical and pathological data.

Positive survivin expression was found in 209 of 299 cases of HNSCC (69.90%). Staining was negative in 90 (30.10%) cases, weak in 168 (56.19%), moderate in 40 (13.38%) and strong in 1 (0.33%) case. A homogeneous staining pattern was seen in all specimens (nuclear staining with percentage of stained cells > 50% for positively stained specimen). Survivin was significantly overexpressed in tumour tissue whereas no survivin expression was detected in normal tissue (control).

Representative images showing survivin expression in samples of HNSCC are shown in Fig. 1.

Significant differences in expression could not be detected between the HNSCC subsites OSCC, OPSC and LSCC.

Regarding the results of the whole series of HNSCC cases examined, statistical analysis revealed significant correlations between survivin expression and pT stage (pT1, pT2 versus pT3, pT4) ($p = 0.018$) and pN stage (pN0/pN1 versus pN2, pN3) ($p = 0.030$).

A strong correlation between pM stage ($p = 0.0266$) and survivin expression was also found.

Influence on overall and recurrence-free survival rates

The data from all cases, including all subsites of the head and neck, showed that recurrence-free survival was independent from survivin expression levels.

Survivin expression in HNSCC (at all tumour subsites) was significantly correlated with overall survival ($p = 0.0068$) (Fig. 2). In the HNSCC subsites (oral cavity, oropharynx, larynx), no correlations between overall survival and recurrence-free survival were noticed.

Correlations in HNSCC subsites

There was a significant correlation between survivin expression (survivin pos. versus survivin neg.) and the pM status ($p = 0.025$) in HNSCCs of the oral cavity.

In the oropharyngeal subsite, the tumours showed a higher survivin expression in locally advanced tumours (pT3/pT4 versus pT1/pT2) with a significance level of $p = 0.018$.

Most of the clinicopathological correlations were found within the subsite of LSCCs. In these tumours, statistically significant correlations could be found between pN staging (pN 0–3) and the survivin expression patterns (moderate, weak and negative expression) ($p = 0.0163$). Furthermore, there was a highly significant correlation between pN positive LSCC and survivin expression patterns ($p = 0.008$). Similar to the results over all HNSCC subsites, the pT status correlated with positive/negative survivin expression in LSCCs when comparing locally advanced tumours (pT3/pT4) with local tumours (pT1/pT2) ($p = 0.030$).

Discussion

Head and neck squamous cell carcinoma is a devastating disease, affecting 500,000 new patients per year globally and is the sixth most common malignancy worldwide, accounting for more than 90% of head and neck cancers [31]. It involves the upper aerodigestive tract and can affect the structure and function of organs involved in voice, speech, taste, smell and hearing, as well as vital structures necessary for survival [32, 33]. HNSCC constitutes a noteworthy growing public health problem and is a major cause of mortality [34].

Despite modern disease management with strategically designed clinical trials, diagnostic and innovative approaches, the 5-year survival rate for HNSCC has not improved significantly over the past decades [35]. Furthermore, loco-regional relapse following therapy is a major cause of death [7]. The prognostication of patients with HNSCC is extremely variable but essential for reducing deaths due to head and neck cancer [1]. Therefore, validating distinct biological prognostic markers that signal an increased risk of treatment failure, which will have a significant impact on the treatment modalities as well as the intensity of post-treatment follow-up, should be a high priority for improving quality of life in HNSCC patients.

Interestingly, survivin is strongly expressed in HNSCC and its multifaceted oncological role in various cellular pathways of different cancers, including head and neck cancer, has placed this IAP agent as a safe and ideal target for oncological research [10, 35]. Herein, we demonstrate its mechanistic action in HNSCC. The aim of the present study was to show survivin expression in HNSCC. Further we followed the hypothesis survivin expression to be of prognostic/predictive importance. Significant positive correlations with tumour stage, regional and distant metastases were observed. Furthermore, we could also show local differences in the expression patterns. The subgroups of OSCC and LSCC showed especially significant correlations between survivin expression and tumour stage. Additionally, LSCCs showed a correlation between survivin and nodal stage. Reports of survivin and its relationship with clinicopathological stages are sparse. Our findings support the results of another group which analysed a much smaller cohort of HNSCCs [5]. Compared with the report by Pickhard et al. [5] our analysis demonstrated a significant relationship with survival in the whole cohort. However, our subgroup analysis did not show any significant differences regarding survival for overall or recurrence-free survival. Unfortunately, Pickhard et al.[5] did not give any detailed information about the survival data (e.g. which specimens were included/excluded) and did not mention a subgroup analysis. Our findings do support the investigations of other groups looking at the function of survivin and its effect on therapy response [36].

It was recently reported that survivin facilitates HNSCC growth, which is supported by our results regarding the association with higher tumour stages, which are directly affiliated

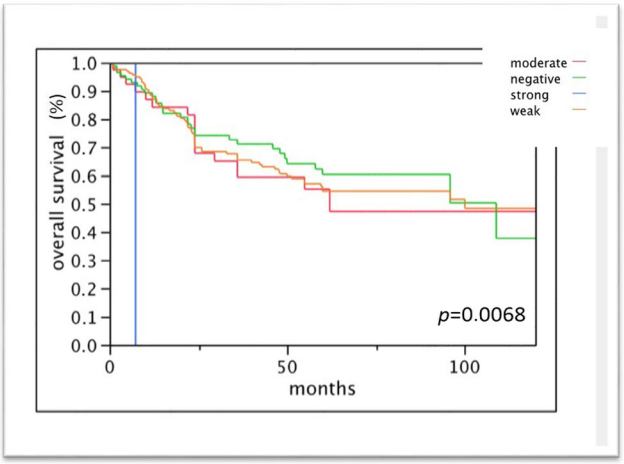

Fig. 2 Kaplan–Meier curves for survivin expression for overall survival

with tumour size [37]. In addition to its prognostic relevance, survivin may also be an important therapeutic target [38]. Zhang et al. looked at sepantronium bromide (YM155), a selective survivin suppressant that induces apoptosis and autophagy. They showed that YM155 in combination with docetaxel promoted tumour regression in a xenograft model [38]. Increased levels of survivin in malignant tissues, therefore, indicate the existence of a therapeutic platform for potential antisurvivin therapies, facilitating the diagnosis and treatment of cancer. Thus, it can be concluded that survivin is a potentially useful prognostic tumour biomarker for current treatment regimes, and its expression may play a key role in predicting the long-term clinical outcome and quality of life in HNSCC patient; it may preclude unnecessary treatments. In addition, survivin is potentially a new target for improving the outcome of chemotherapy. Further research is needed for clinical management and prognosis to understand and corroborate the novel targets, i.e. prognostic markers for individualising preventive therapeutic management and predicting disease progression in patients with HNSCC. This may lead to a more favourable anticancer therapeutic strategy and survival outcome. The big advantage of our study is the first presentation of a large cohort of HNSCC examined for survivin expression and compared to clinical data. In the last years, HNSCC oncologist had to learn the inter-tumour differences. OPSCC, not only regarding the HPV presence, seem to have different pathways in tumour development. It is of importance to approach the HNSCC subtypes as different entities. This study could show the importance of survivin. With our data collection, we were not able to look at the subtypes and different therapies.

Conclusion

Survivin expression correlates with survival and clinical parameters in HNSCCs. On the cellular level, these results are

very promising and worth concentrating our efforts on the molecular level. Additionally, a bigger cohort of patients will be examined and hopefully we will be able to address the prognostic value of survivin expression related to the various treatment approaches and different tumour localisations in HNSCCs.

Funding The work was supported by the Institute of Pathology and the Department of Otolaryngology, Head and Neck Surgery at the University Medical Centre Hamburg-Eppendorf.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

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