The effects of anesthesia on the morphoproteomic expression of head and neck squamous cell carcinoma: a pilot study

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The prognosis and disease-free survival rates for head and neck squamous cell carcinoma (HNSCC) have remained relatively stagnant for the last several decades. Moreover, as is the case with other malignancies, locoregional recurrence and distant metastasis are all too common even after seemingly successful oncologic surgery and adjuvant therapy. Recently, increased focus has been placed on understanding the influence of perioperative factors on tumor cell behavior and surgical outcomes. More specifically, emerging research suggests that anesthetic agents may play a role in cancer recurrence by interacting with prosurvival protein signaling pathways which harden tumor cells against oncologic treatments. In the present pilot study, we tested the hypothesis that inhalational anesthesia and total intravenous anesthesia (TIVA) exert differential effects on the proteomic expression of HNSCC. Ten patients with previously untreated oral cavity or oropharyngeal HNSCC were randomized to receive either sevoflurane and remifentanil or propofol and remifentanil for the duration of their respective surgeries. Morphoproteomic analysis using 10 pro-oncogenic protein markers was performed on both pre- and postanesthesia tumor samples to qualitatively grade changes in protein expression. The results of this analysis demonstrated differential expression of several protein markers. Specifically, the exposure to sevoflurane but not TIVA resulted in a statistically significant increase in the expression of cytoplasmic hypoxia-inducible factor-2alpha ($P = 0.049$) and nuclear p-p38 mitogenic-activated protein kinase ($P = 0.041$). This study represents one of the first to evaluate the effects of anesthesia on the molecular biology of HNSCC in vivo, and the results suggest that the exposure to sevoflurane may increase the expression of pro-oncogenic protein markers in HNSCC tumor cells. (Translational Research 2015;166:674–682)

Abbreviations: HNSCC = head and neck squamous cell carcinoma; TIVA = total intravenous anesthesia; MAC = minimum alveolar concentration; NSAID = nonsteroidal anti-inflammatory drug; HIF-1α = hypoxia inducible factor 1 alpha; HIF-2α = hypoxia inducible factor 2 alpha; SIRT1 = sirtuin 1; p-mTOR = phosphorylated mammalian target of rapamycin; FAS = fatty acid synthase; p-p38 MAPK = phosphorylated (p)-mitogen activated protein kinase; COX-2 = cyclooxygenase 2; p-c-Met = phosphorylated MET proto-oncogene tyrosine kinase receptor; p-Akt = phosphorylated protein kinase B (Akt); p-NF-κB = phosphorylated NF- kappa B

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AT A GLANCE COMMENTARY

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Background

For patients with head and neck squamous cell carcinoma, disease recurrence is all too common despite seemingly successful oncologic surgery. Contemporary research has begun focusing on the impact that perioperative factors, such as the type and method of anesthesia used, may have on cancer recurrence and outcomes. More specifically, several studies have shown that inhalational anesthetics upregulate prosurvival cellular pathways.

Translational Significance

The present study used morphoproteomic techniques to evaluate the effects of inhalational vs intravenous anesthesia on head and neck squamous cell carcinoma tumor cells in vivo. Our preliminary results demonstrate differential expression of several prosurvival proteins and add to the growing body of evidence suggesting that anesthetic agents may affect oncologic surgical outcomes.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) remains a common form of cancer worldwide with approximately 500,000 new cases diagnosed annually.[1] Surgical ablation is the primary mode of treatment in a majority of cases and is often supplemented with adjuvant radiation or chemoradiation. Although the last several decades have seen great advancements in oncologic treatments, disease-free survival rates for HNSCC have remained largely stagnant.[2,3] Locoregional and distant recurrence are frequent after seemingly successful surgical resection, and patient outcomes and prognosis after salvage procedures remain poor. This dichotomy of disease recurrence after complete surgical resection has led to inquiry into the impact that perioperative factors may have on tumor recurrence. Several in vitro studies[4,5] have demonstrated that various anesthetic agents interact with normal and malignant tissues at the cellular and molecular levels. Specifically, inhalational anesthetic agents have been shown to alter the expression of several prosurvival cellular proteins that could potentially affect the success of oncologic treatments.[6]

The role of tumor genomic and proteomic expression on prognosis and patient outcomes is only beginning to be understood. The emerging science of morphoproteomics promises to improve patient outcomes by enabling the use of targeted therapies based on a specific tumor's unique molecular profile. Its application has been validated in several different malignancies and has been recently demonstrated in HNSCC.[7] In this study, we tested the hypothesis that anesthetic agents, specifically inhalational forms, differentially affect the expression of tumor-related, prosurvival cell signaling pathways. Morphoproteomic analysis was used to evaluate the differential expression of known tumor-related proteins in patient tumor specimens after the exposure to inhalation and intravenous anesthesia in vivo.

MATERIALS AND METHODS

Recruitment of patients with oral cavity or oropharyngeal squamous cell carcinoma. Approval for the study was obtained from our institutional review board (HSC-MS-13-0187). Furthermore, the study protocol adhered strictly to the guidelines for human subject research as outlined in The Code of Ethics of the World Medical Association, and all subjects provided written informed consent before study participation. All adult (>18 years) patients with previously untreated squamous cell carcinoma of the oral cavity or oropharynx presenting to either our outpatient clinic or university-based hospital were considered eligible for study inclusion. Ten patients with operable tumors were recruited and subsequently randomized to receive either sevoflurane-remifentanil (5 patients) or propofol-remifentanil (5 patients) for the duration of their procedures. On recruitment into the study, each patient was de-identified and assigned a number (ie, 1–10). Random assignment into 1 of the 2 anesthesia protocols was then performed based on an electronic, algorithmic randomization process. Finally, both patients and the operating surgeon were blinded to the type of anesthesia administered.

Exclusion criteria were recurrent or previously treated disease and surgically unresectable tumors. Furthermore, patients with medical comorbidities that would be expected to require high FiO_2 during surgery, patients at high risk for perioperative hypoxic events, and patients whose total anesthesia exposure time was anticipated to be less than 2 hours were also excluded from the study. This minimum exposure time requirement was based on prior in vitro studies[8,9] which demonstrated that cellular genomic and proteomic alterations can be reliably detected after this duration of anesthesia exposure. All surgical procedures were performed at a single clinical site by a single surgeon (R.J.K.).