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Otolaryngology Cancer Stem Cell Signalling in Head and Neck Cancer Repopulation

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Abstract

Patients with head and neck cancer (HNC) experience treatment-related issues that may degrade their health and quality of life (HRQOL). The purpose of this study was to describe the functional status factors and shoulder pain symptom experience that is related to general and domain-specific HRQOL at one month after HNC surgery. In this early study, 29 patients were examined. Overall HRQOL as well as the physical, functional, emotional, and social wellbeing were considered outcome factors. The existence of symptoms and characteristics affecting functional status served as the independent variables.

The objective of the study was to investigate cancer stem signalling during the repopulation response of a head and neck squamous cell carcinoma (HNSCC) xenograft after radiation therapy. The xenografts were made using low passage HNSCC cells, and either sham radiation or 15 Gy in one fraction were then applied to them. Three tumours from each group were collected at various time points for the investigation of global gene expression, pathway analysis, and immunohistochemical evaluation, including days 0, 3, and 10 for controls and days 4, 7, and 12 and 21 after radiotherapy. Following radiation, 316 genes were discovered to be associated with many genes related to stem cells and to exhibit differential expression (p 0.01 and 1.5-fold) at least once in UT-SCC-14 xenografts.

Keywords: Xenografts; Neck cancer; Head cancer; Tumor

Introduction

Up to 80% of patients with head and neck cancer (HNC) experienced shoulder pain after neck lymph node dissection, which adversely affected shoulder function. Among the cancers of the head and neck are malignant tumours of the larynx, pharynx, thyroid, salivary glands, nose, and nasal passages. Treatment for HNC has a negative impact on one or more basic functions, such as speaking, eating, breathing, and body image because of the specific anatomic structures implicated. It is projected that there will be 113,860 new cases of head and neck cancer in 2013 [1].

Shoulder pain, shoulder dysfunction, negative body image, and difficulty breathing, eating, or speaking all contribute to decreased health-related quality of life (HRQOL). Along with survival and recurrence, HRQOL has been considered one of the most important outcomes in HNC research. Despite the fact that there is no widely accepted instrument to measure HRQOL, the majority of researchers agree that HRQOL is a subjective and multidimensional construct made up of four major domains in a person's health-related life: physical well-being, functional well-being, emotional well-being, and social well-being [2].

When compared to retreatment baseline data, HRQOL in HNC patients immediately dropped after cancer therapy, according to longitudinal research. A key strategy for helping HNC patients cope with and adjust to the long-term adverse effects of cancer treatment is early rehabilitation. However, descriptive research is necessary to inform clinicians about the significance of identifying HNC patients with shoulder pain and diminished body functions, both of which increase their risk for having poor HRQOL, before interventions can be developed to improve HRQOL in the early postoperative period [3]. The conceptual framework for this study was developed using empirical data and the Symptom Management Model from the University of California, San Francisco School of Nursing. The UCSF-SMM was created by researchers to define the two connected variables "symptom experience" and "outcomes," which are two connected variables. "Symptom experience" has previously been defined as symptom intensity and symptom distress, but it has also been evaluated as a single symptom or as a collection of symptoms. Studies have revealed functional status and quality of life as "outcomes" that are connected to "symptom experience," which can both have an impact on one another. Using the WHO's International Classification of Functioning, Disability, and Health, functional status has been operationalized in the HNC research [4].

It is well known that spinal accessory nerve damage sustained during neck dissection, which results in either temporary or permanent denervation of the trapezius muscle, causes shoulder pain and impaired shoulder function. We used neck dissection as one of the inclusion criteria. In our study, UCSF-SMM concepts and empirical data were used to describe the relationships between shoulder discomfort, impaired body functions, and HRQOL after HNC surgery. The study's main outcome is HRQOL. The four domains of physical, functional, emotional, and social well-being, along with emotional and social well-being, were the four outcome variables that made up the overall HRQOL. The functional status characteristics and symptom experience were categorised as independent variables. Following HNC surgery, shoulder soreness served as the standard by which symptoms were described [5].

The origin of the heterogeneous collection of cancers known as head

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and neck squamous cell carcinomas (HNSCCs) is the mucosal lining of the upper aero digestive tract. Despite advances in medicine, survival rates have remained stable for a while. Histological, phonotypical, and karyotypical examinations have shown that the heterogeneity of HNSCC has primarily been attributed to the clonal growth process. It is now commonly acknowledged that not all cancer cell heterogeneity is genetically determined and that cells within a single tumour clone have a wide range of potentials for cell proliferation and tumour formation. According to the notion, the bulk of cancer cells lack the ability to divide and only a tiny number of phenotypically distinct cells do.

Loco regional progression is the primary cause of treatment failure and cancer-related death in advanced, inoperable HNSCC treated with radiation or chemotherapy. The population's response to radiation will be a major limiting factor for curability if CSCs have the tendency to repopulate tumours after therapy. In a variety of cancers, research has demonstrated that CSCs are more radiation resistant than their non-CSC counterparts, and many studies, including HNSCC, have demonstrated a relationship between CSCs and chemo resistance.

In this study, we developed a model of local failure and repopulation in an HNSCC xenograft using a sub curative dose of radiation, and used global gene expression at significant tumour response time points to examine the changes in protein expression of known stem cell-related genes as well as stem cell-related signalling pathways [6].

Materials and Methods

Sample and Setting: This descriptive, correlational study used a convenience sample of 29 head and neck cancer patients drawn from a Midwestern hospital. The initiative received approval from the institutional review boards of the university and hospital. Data were collected one month following HNC surgery using self-administered surveys and physical examinations. A participant had to have had their first neck dissection surgery, be able to converse in English, and be able to give informed consent in order to be included in the study. Patients with restricted range of motion or current shoulder discomfort were not candidates for surgery.

Measures

Age, gender, race, marital status, educational attainment, and employment position were all gathered using a demographic survey. Participants were asked to self-report how much they now consume in terms of alcohol and smokes. The primary cancer site and stage were determined from medical data. To collect the outcome and independent factors, a self-administered survey and a physical examination were both used.

Cell Line, Xenograft, and Irradiation

The Finnish University of Turku's Dr. R. German provided the UT-SCC-14 cell line. It was picked from a huge panel of head and neck cancer cell lines derived from primary and recurrent tumors. The cell line has been maintained at low passage number to maintain phenotypic and morphological features identical to the primary tumour, which was a T3N1M0, moderately differentiated, HPV-negative oral tongue squamous cell carcinoma. The experimental plan was approved by the animal care committee at William Beaumont Hospital. The NIH III female, nude mice utilised in this study ranged in age from four to six weeks [7].

Experimental Design

The UT-SCC-14 cell line was purchased from Dr. R. Grénman, University of Turku, Finland, and was selected from a sizable panel of cell lines derived from primary and recurrent malignancies of the head and neck region. The cell line is a T3N1M0, moderately differentiated, HPV-negative oral tongue squamous cell carcinoma that has been preserved at a low passage number to preserve its parent tumour's phenotypic and morphological characteristics. The experimental idea was approved by the animal care committee at William Beaumont Hospital. Female NIH III naked mice between the ages of 4 and 6 weeks were used in this research.

Isolation of RNA and Gene Expression

Laser capture micro dissection was used to remove cells from the tumour's periphery in accordance with our earlier observation of core necrosis after radiation therapy. Using OCT (Tissue-Tek; Sakura Finetek, USA), eight micrometre sections of frozen tissue samples were cut and mounted onto glass slides with PEN (polyethylene naphthalene) membranes (two sections per slide). On comparable tissue slice H&E slides, peripheral areas were detected. The stained slides were micro dissected onto Cap Sure Macro LCM Caps with a Micro dissection System within two hours of sectioning (Molecular Devices). To isolate the RNA, the RNeasy plus Micro Kit was utilised (Qiagen, Valencia, CA). The Model 2100 Bio analyser and ND-8000 spectrophotometer used to measure RNA concentration and quality were donated by Nano Drop Technologies, Inc. of Wilmington, Delaware.

Data Analysis

The raw intensity data from the Affymetrix GeneChip arrays was imported into the Partek Genomics Suite, which then used the robust multichip average to normalise the data and summarise the median polish probeset. Quantile normalisation, log2-transformation, background adjustment for guanine-cytosine concentration, and quantile normalisation were also performed during this process. Exons were then compressed to genes using the average of the probe sets. Differentially expressed genes were discovered by using 1-way ANOVA to compare samples from a certain irradiation time point to the controls [8].

Procedure

Both the university's and the healthcare system's institutional review boards have given this study their blessing. A nurse practitioner who was in charge of providing direct care to this patient population chose potential participants who had undergone HNC surgery and introduced them to the study. An investigator visited patients in their private hospital rooms within 24 to 48 hours of their release if they gave permission to be approached. The researcher clarified any questions, answered concerns, and assessed interest in participating. 34 patients expressed interest, but only 29 (85%) were approved due to their eligibility. The next step was to arrange for data to be collected at the same time as their surgeon's routine 30-day follow-up appointment [9].

Results

Tumor Characteristics, Growth Rate, and Response to Radiation

The untreated UT-SCC-14 xenografts had a volume doubling time of 4.8 0.7 days, whereas the radiation-treated tumours showed a significant growth halt up until day 12, at which point they began to repopulate. We discovered that core coagulate necrosis with pyknotic nuclei characterized early radiation necrosis (days 4–12), whereas widespread necrosis with fragmentation and dystrophic

calcifications characterized late radiation necrosis (days 12-onwards). The histology studies that demonstrated that repopulation of the tumour occurred from the periphery region led to the restriction of the immunohistochemistry and gene expression research to only this region in the control and treated animals.

Specific Gene Expression Changes Associated with Stem Cell Signalling

Three genes, CTNNB1, MMP9, and NOTCH1, were found in the pathways of all nine stem cell-associated genes. While MMP9 was unregulated at days 12 and 21, NOTCH1 was down regulated at days 12 and 21, but CTNNB1 was only enhanced at day 4. IL6, IL8, and SMAD2 were three of the nine signalling pathways' nine genes. IL6 and IL8 levels were raised at day 12, but SMAD2 was only unregulated at day 7. The seven genes that were found in seven out of the nine pathways were ICAM1, LIF, MAPK8, MET, SPP1, TGFA, and TGFBR2. MET and TGFA were increased at key days 7 and 12. Day 12 marked the start of LIF1 and SPP1's expression, although MAPK8 didn't start.

Discussion

The preliminary results of this study focused on the early postoperative symptom experience and functional status factors that are related to HRQOL in patients with HNC. The conceptual framework we proposed in light of the UCSF-SMM and empirical data was only partially supported by the findings. The findings indicated that patients may be at risk for worse levels of HRQOL, particularly in physical and functional well-being, if they had more acute shoulder pain distress, poor eating and speaking abilities, and a negative body image. The HRQOL variables from the current study and the two preceding studies Participants in this research had different types of HNC.

Our analysis was conducted one month after HNC surgery, whereas Rose and Yates' study was conducted more than three years after surgery and/or radiation treatment and one month after radiation treatment. The overall HRQOL scores throughout these three trials were comparable. In the early post-HNC treatments, the participants' emotional and social well-being scores were higher than their physical and functional well-being scores, according to both our study and the study of Rose and Yates. Long-term survivor participants' (>3 years) emotional and social well-being scores were lower than their physical and functional well-being scores. The majority of people concur that the HNSCC comprises CSC populations with self-renewal and differentiation capacities. A greater understanding of the mechanisms driving their dynamics is necessary to properly comprehend the importance and significance of HNSCC CSCs in therapy resistance and disease progression. This work used a model to investigate the molecular changes related to known genes associated with stem cells during the repopulation and regrowth of an HNSCC xenograft after a sub curative radiation treatment. Since a single 15 Gy dose would kill about 90% of the tumour's cells, the basic idea behind this method was that if CSCs were a significant factor in treatment resistance, they would also govern the repopulation response.

Numerous genes, including as CD44, BMI1, c-MET, NOTCH1, ALDH1, and SOX2, have been connected to a poor prognosis in HNSCC. The genes included in this study were chosen because each of them has been connected to CSCs in HNSCC and other cancers. The multifunctional Trans membrane glycoprotein CD44, which also interacts with molecules like fibronectin, fibrinogen, laminin, galectin-8, collagen, chondroitin sulphate, and osteopontin, is a receptor for hyaluronic acid. It has been proposed that HA binding to CD44 promotes CD44-EGFR interaction and EGFR phosphorylation. The most often used cell-surface CSC marker in many other tumour types is CD44, which has also repeatedly been identified as a CSC marker in HNSCC.

The aldehyde dehydrogenase family of enzymes is required for the synthesis of retinoic acid as well as the growth of squamous epithelia. It was found that primary HNSCC cells with high levels of ALDH1 expression were more tumorigenic than those with low expression in the creation of xenografts. Furthermore, numerous studies have shown a connection between ALDH1 overexpression and a bad prognosis. By combining CD44+ and expression, primary HNSCC cells with enhanced xenotransplantation effectiveness were further chosen. HNSCC has been connected to the c-MET receptor tyrosine kinase, which has also been connected to a worse prognosis and responsiveness to therapy. Since a subpopulation of c-MET+ cells were discovered to be more tumor-prone, it has also been linked to CSCs [10].

Conclusion

In conclusion, our study identified early postoperative symptoms of shoulder pain, difficulty swallowing, speaking, and negative self-image in HNC patients. The American Cancer Society promoted early and regular examination of symptoms and impaired bodily function in 2013 across the cancer care continuum. Patients with rehabilitation problems should only be diagnosed and treated by a small number of medical specialists. In order to treat shoulder pain, poor eating and speaking, and altered body image, HRQOL among HNC patients must be well managed. They require a multidisciplinary care team composed of a speech-language pathologist, occupational therapist, physical therapist, and dietician. The oncologist, primary care doctor, and nurse should employ the proper equipment to effectively identify patients' symptoms and damaged physical functioning. No studies have attempted to comprehend the significance of CSCs in the repopulation/regrowth response of HNSCC following radiation therapy, despite the fact that they have been consistently discovered in HNSCC and have been shown to be able to promote tumorigenicity and resistance to chemotherapy. In this study, we have demonstrated that several pathways connected to known stem cell-related genes respond similarly to radiation exposure, which is consistent with the transition from damage healing to regrowth of an HNSCC xenograft in vivo. The work emphasises the importance of epithelial-to-mesenchyme regulators in the process of recovery from radiation-induced DNA damage in addition to highlighting the possible importance of the MET/CD44 axis.

Acknowledgement

None

Conflict of Interest

None

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