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REVIEW ARTICLE

Advancing theranostics with tumor-targeting peptides for precision otolaryngology

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Abstract Worldwide, about 600,000 head and neck squamous cell carcinoma (HNSCC) are detected annually, many of which involve high risk human papilloma virus (HPV). Surgery is the primary and desired first treatment option. Following surgery, the existence of cancer cells at the surgical margin is strongly associated with eventual recurrence of cancer and a poor outcome. Despite improved surgical methods (robotics, microsurgery, endoscopic/laparoscopic, and external imaging), surgeons rely only on their vision and touch to locate tumors during surgery. Diagnostic imaging systems like computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) are too large, slow and costly to use efficiently during most surgeries and, ultrasound imaging, while fast and portable, is not cancer specific. This purpose of this article is to review the fundamental technologies that will radically advance Precision Otolaryngology practices to the benefit of patients with HNSCC. In particular, this article will address the potential for tumor-targeting peptides to enable more precise diagnostic imaging

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while simultaneously advancing new therapeutic paradigms for next generation image-guided surgery, tumor-specific chemotherapeutic delivery and tumor-selective targeted radiotherapy (i.e., theranostic).

Abbreviations

^{18}F-FDG	Fluorine-18-fluorodeoxyglucose
^{64}Cu	Copper-64
^{68}Ga	Gallium-68
^{89}Zr	Zirconium-89
^{90}Y	Yttrium-90
^{111}In	Indium-111
^{123}I	Iodine-123
^{124}I	Iodine-124
^{131}I	Iodine-131
^{177}Lu	Lutetium-177
CLI	Cerenkov luminescence imaging
CPP	Cell-penetrating peptide
CR	Cerenkov radiation
CT	Computed tomography
Cy5	Cyanine 5 dye
DT	Diphtheria toxin
EGF	Epidermal growth factor
FITC	Fluorescein isothiocyanate
GC	Gamma camera
HN-J	HN-Jumbled
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
ICG	Indocyanine green
MRI	Magnetic resonance imaging
NIR	Near-infrared
OSN	Optical surgical navigation
PET	Positron-emission tomography
PKCε	Protein kinase Cε
SPECT	Single-photon emission computed tomography
siRNA	Small interfering RNA

Squamous cell carcinoma and the roles of conventional imaging and advanced molecular imaging

There are approximately 600,000 new cases of HNSCC worldwide each year consisting of both high risk HPV+ and HPV− malignancies.[1,2] Routine surgical resection is used for definitive treatment of HNSCC tumors and is currently guided only by the surgeon's vision and palpation. The current treatment paradigm begins with pre-operative surgical planning using conventional diagnostic imaging (CT, MRI and/or PET) imaging followed by targeted visual resection of the lesion(s) as well as concerning lymph nodes. Due to the associated complex anatomy, complete resection of HNSCC is often arduous with little or no real-time verification of complete surgical resection. The standard histopathologic assessment of resected surgical specimens and their margins can take several days to complete. Not uncommonly, surgeons are notified days later that positive surgical margins exist in the resected specimens. Following definitive unguided surgical resection, recurrent malignancy occurs in 10%–26% of HNSCC patients within 5 years, which suggests that some degree of residual malignancy remained after surgery.[3] The presence of residual malignancy within the surgical bed indicates that local tumor recurrence is likely and is a poor prognostic factor.[4] In addition, the total number of histologically malignant lymph nodes removed during the concurrent neck dissections is a risk factor for local recurrent malignancy as well as distant metastases.[3,5] The overall survival rate for HNSCC patients has not significantly improved during the last 20 years with locoregional tumor recurrence/relapse and distant metastases representing the primary causes of morbidity and mortality.[6]

The ability to detect and completely resect the primary malignancy as well as adequately evaluate for associated metastatic lymph nodes are critical factors in determining patient prognosis and subsequent adjuvant therapies. With respect to conventional imaging assessment for patients with HNSCC, contrast-enhanced CT or MRI of the site of primary malignancy in the head and neck is performed, as well as chest imaging, as part of the initial clinical evaluation. Advanced molecular imaging using Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT or PET/MRI may also be performed to evaluate the primary tumor and assess for locoregional and distant metastatic disease. ^{18}F-FDG PET is used for the diagnosis, staging, and restaging of HNSCC patients. Unfortunately ^{18}F-FDG PET has a false positive rate of 23%–30% in HNSCC patients,[7–10] which may necessitate further diagnostic evaluation and tissue sampling as well as potentially delaying therapy. These current limitations and the critical need for improved diagnostic, quantitative and prognostic stratification of HNSCC patients before, during and after definitive therapy are recognized by the interdisciplinary treatment team.

Peptides and antibodies as potential HNSCC imaging agents

A promising approach to improve both diagnostic sensitivity/specificity and definitive therapy is the evolving field of tumor-targeting peptides and antibodies. The angiogenic cyclic RGD peptide cilengitide was one of the first promising peptides which specifically targeted the $\alpha_v\beta_3$ integrin receptor associated with highly vascular tumors like HNSCC.[11,12] Recent work in BcaCD885 tumor-bearing mice