Metastatic Anal Cancer and Novel Agents

Van Morris, MD, Cathy Eng, MD*

KEYWORDS

• Anal cancer • Squamous cell • Chemotherapy • Immunotherapy • HPV • PD-1

KEY POINTS

- Squamous cell carcinoma of the anal canal (SCCA) is a rare, understudied disease that can be cured by concurrent chemoradiation in the nonmetastatic setting.
- No consensus standard-of-care approach to the treatment of metastatic SCCA exists to date; cytotoxic doublet chemotherapeutic doublets have traditionally been utilized for metastatic disease.
- Early results from trials incorporating immune checkpoint blockade agents for the treatment of metastatic SCCA hold great promise for improving survival outcomes for patients with this disease.

INTRODUCTION

Anal cancer represents a rare disease that accounts for approximately 2% of all gastrointestinal (GI) malignancies.[1] Although most patients will present with locoregional disease, a fraction of patients will develop distant metastases.[2–4] This article focuses on the management of metastatic disease of anal cancers of squamous cell histology and not of other underlying histologies like adenocarcinoma or anal melanoma. Previous experiences with systemic chemotherapies and local therapies for oligometastases will be discussed, as will the role of emerging immunotherapy agents as a novel approach to the treatment of distant metastases.

EPIDEMIOLOGY

Over 90% of anal cancers are of squamous cell histology. In 2016, it is estimated that over 8000 new cases of squamous cell carcinoma of the anal canal (SCCA) will be diagnosed in the United States, with over 1000 deaths from this disease.[1] The annual incidence of SCCA continues to rise, both in the United States and globally, and it is

The authors have nothing to disclose.
Department of Gastrointestinal Medical Oncology, The University of Texas – MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, TX 77030, USA
* Corresponding author.
E-mail address: ceng@mdanderson.org

Surg Oncol Clin N Am 26 (2017) 133–142
http://dx.doi.org/10.1016/j.soc.2016.07.008
surgonc.theclinics.com

expected that this trend will continue for decades to come.[5] Risk factors for the development of anal cancer include a prior history of gynecologic malignancy, tobacco use, a history of multiple sexual partners, and impaired immunity, whether from use of immunosuppressive agents, underlying autoimmune disease, or from coexisting human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).[6–10]

However, by far the most prevalent factor responsible for the development of SCCA is coinfection with human papilloma virus (HPV).[8,11,12] This virus also plays an important role in other malignancies such as squamous cell carcinoma of the head and neck, cervical cancer, vaginal/vulvar cancer, and penile cancer.[13–20] Incorporation of viral DNA into the host cell genome results in expression of the viral oncoproteins E6 and E7, which disrupt p53 and Rb, respectively, to promote oncogenesis.[21–23] In a series of patients with metastatic SCCA treated at the authors' institution, the presence of HPV, assessed by the detection of HPV by DNA in situ hybridization and/or p16 by immunohistochemistry, occurred in over 95% of tested tumors.[24] Other groups have also reported that most anal cancers are associated with HPV infection,[25,26] and it appears as though the presence of HPV serves as a positive prognostic biomarker from these reports, a trend that is similar to outcomes in other HPV-associated malignancies.

HPV-16 is the most common subtype of HPV associated with the development of SCCA.[27] In recent years, preventative quadrivalent and nonavalent vaccines against the most common subtypes of HPV have been introduced to children and adolescents with no prior HPV exposure. Initial reports with this primary prevention approach in adolescent girls have suggested success rates in lowering the incidence of precancerous cervical lesions.[28,29] Applied to SCCA, 1 prospective study demonstrated that, in a population of men who have-sex with men, use of preventative vaccines against HPV led to lower rates of anal dysplasia.[30] These data have not fully matured to demonstrate lower rates of anal cancer with such vaccines, although updated results are greatly anticipated. The authors suspect that in the decades to come, a generalized trend toward decreased prevalence/incidence of SCCA will occur as the result of these HPV vaccines.

MANAGEMENT OF LOCOREGIONAL SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL

Most patients with newly diagnosed SCCA will present with locoregional disease that has not spread to distant organs. For these patients, the standard of care approach has not changed for decades. Here, patients receive concurrent chemoradiation with either 5–FU/mitomycin C or with 5–FU/cisplatin.[31–35]

Although concurrent chemoradiation is successful in curing SCCA in the majority of patients, approximately 10% to 30% of this population will develop a locoregional failure with recurrent disease at the site of the primary tumor.[2,36] Risk factors for recurrence include a primary tumor greater than 5 cm in longest dimension, the presence of regional lymph nodes at diagnosis, and male gender.[3] For such patients who recur after chemoradiation, the standard of care is abdominoperineal resection (APR),[36] which has a success rate with respect to 5-year survival of approximately 40% to 65% following surgery, despite the presence of a tumor that was not eradicated upfront by chemoradiation.[37–39]

MANAGEMENT OF METASTATIC SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL WITH CYTOTOXIC CHEMOTHERAPY

Because SCCA represents an uncommon GI malignancy for which a small fraction of patients will develop distant metastases, the role of systemic chemotherapy in the