

BACKGROUND

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer diagnosed in the United States (1). Over 500,000 new cases of HNSCC are diagnosed worldwide each year (2). Unfortunately, with the development of new therapeutic modalities little change has been seen in the overall survival of patients leaving significant work to be done.

The utility of induction chemotherapy in the treatment of head and neck cancer remains controversial. There has been a multitude of small studies that have demonstrated its potential benefit over current mainstays of treatment. However, these studies have yet to be statistically correlated at scale. Large studies have shown mixed results. The majority of studies targeted locoregionally advanced cancers of all sites in the head and neck. They have failed to separate by HPV status or primary tumor site. HPV negative oral cavity and oropharyngeal cancers remain most strongly associated with more traditional risk factors for head and neck cancers, including cigarette smoking. Cancers not associated with HPV have poor 5 year overall survival (OS) when treated with conventional therapy. Additionally, while the advent of HPV related cancers has caused major shifts in both the epidemiology and prognosis of oropharyngeal cancers, this effect has not been observed in cancers of the oral cavity. As such, HPV negative tumors need to be approached discretely from HPV positive cancers of the oropharynx.

Induction chemotherapy has indications for each site in head and neck cancer but must be understood according to site. With regards to HPV- tumors of the oral cavity and oropharynx, induction chemotherapy provides several benefits, including survival and reduced morbidity of treatment. The greatest limitation to the use of induction chemotherapy in the treatment of locoregionally advanced cancer has to do with the toxicity of chemotherapy. This study addresses the above benefits and concerns, with the finding that with careful patient selection, and with appropriate treatment regimen and intent, induction chemotherapy can provide all the above benefits without untenable side effects.

METHODS

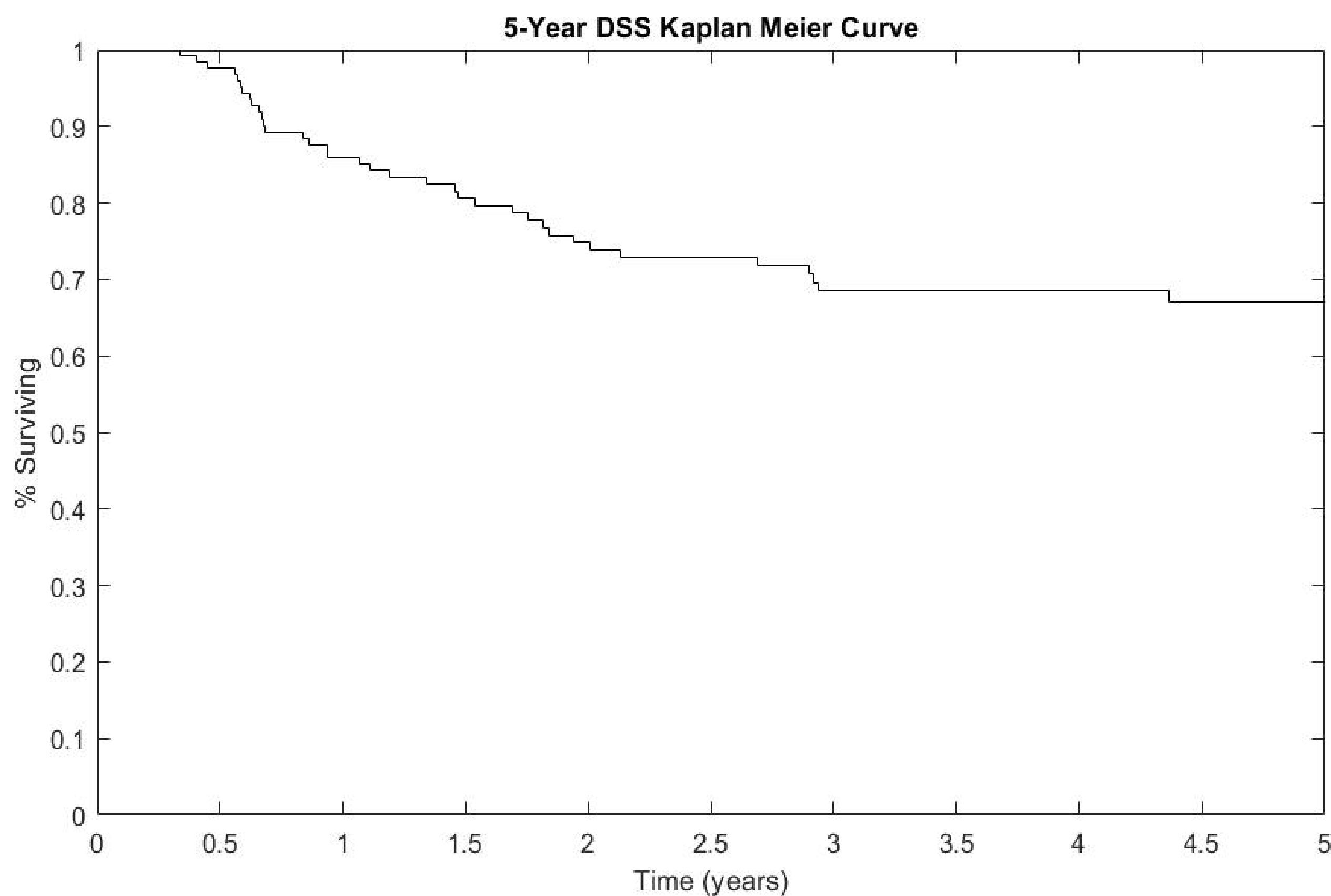
A retrospective review of all treatment naïve patients with locoregionally advanced HPV – oral cavity and oropharyngeal cancers treated between 2005 and 2019 was conducted. Patients were excluded if they had distant metastasis at presentation. All patients received a regimen of presurgical chemotherapy inclusive of cisplatin and docetaxel (TP) of 1-5 cycles followed by surgery with or without postoperative adjuvant (chemo)radiation. Adjuvant (chemo)radiotherapy could be deferred if patients had complete response (CR) to induction chemotherapy at the primary and neck; CR in the neck and partial response (PR) at the primary with negative surgical margins or had N1 disease preoperatively and postoperatively without adverse histopathologic features. There were 122 total patients. Mean age was 59 with 89 active smokers, 16 former smokers and 17 non-smokers. 8 patients had stage two disease, 14 stage three and 100 stage four. The most common primary site was the oral tongue. Mean follow-up time for surviving patients was 4.3 years.

RESULTS

90% (110/122) of patients had either significant (>50% tumor necrosis) partial or complete response to induction chemotherapy. There were no grade IV complications or deaths during induction chemotherapy. There were 9 (7.3%) grade III complications. 9 (7.3%) patients required dose reduction during induction chemotherapy. 52% (63/122) patients received adjuvant, postoperative (chemo)radiotherapy following surgery. 20% (25/122) of patients did not receive adjuvant (chemo)radiotherapy due to refusal, prior radiotherapy, death prior to initiation of adjuvant therapy, or other constraints. 29% (35/122) patients suffered recurrence, of which 8 (6.6%) had distant metastasis. 4 of 17 patients (11%) with local recurrence only were salvaged. Response to chemotherapy was strongly predictive of survival and recurrence (p<.02).

86 patients (86/122, 70.5%) are NED (no evidence of disease) or DOC (dead of unrelated causes) at most recent followup. 81 patients are NED or DOC without recurrence leading to a disease-free survival (DFS) of 66%. Of the 36 patients DOD (dead of disease), 30 died of recurrence, 3 died postoperatively, and 3 died during adjuvant (chemo)radiotherapy. There were 35 (28.7%) recurrences, of which only 4, all local recurrences, were salvaged (4/17, 23.5%). Mean time to recurrence was 11.4 months (5-43 months, median 11.2 months). Attempted salvage therapy for all recurrences consisted of chemotherapy, surgery and/or radiation, and varied according to patient. 8 patients (6.6%) had distant metastasis. All of these also had neck recurrences. There were no isolated distant metastases. Disease specific survival (DSS) was not statistically impacted by sex, age at diagnosis, tumor primary site, T stage, N stage, group stage, smoking status, alcohol use, induction regimen, receipt of adjuvant chemoradiotherapy or number of cycles of induction chemotherapy.

Complications During Induction Chemotherapy			
Complication	Number	Causative Regimens	Description
Grade III Dehydration	5	3 TPF, 1 TP 1 TPE	All required cessation of induction chemotherapy
Grade III Pneumonia	3	3 TP	Two completed induction chemotherapy without dose reduction
Grade III Neutropenic Fever	1	1 TP	
Grade II Nausea/Diarrhea	9	5 TP, 4 TPF	All required dose reduction after first cycle of induction, but completed planned number of cycles



T3N1M0 patient throughout induction chemotherapy: (1) Tumor at presentation; (2) Tumor after first cycle of TP; (3) Tumor prior to third cycle of TP; (4) Tumor preoperatively

CONCLUSIONS

This is a large, retrospective series of patients with advanced disease. Induction chemotherapy followed by surgery substantially increases survival in HPV- OCOPC.

- The overwhelmingly, primary driver of prognosis in this otherwise, relatively, homogeneous group of patients was response to induction chemotherapy.
- The morbidity of TP was acceptable in this series without any mortalities noted
- In select patients, adjuvant chemoradiotherapy may be able to defer without sacrificing survival
- The regimen of induction chemotherapy followed by surgery +/- adjuvant chemoradiotherapy appears to have improved survival over historical controls
- The effect of novel immunomodulating and targeted therapies in this subset of patients is unknown
- Further controlled studies are warranted to parse induction in this subgroup of patients to elucidate the degree of benefit

REFERENCES

1. Burke MS, Loree JT, Popat SR, et al. Presurgical Induction Chemotherapy for Squamous Cell Carcinoma of the Tonsil. Laryngoscope. 2019; 00:1-6.
2. Bossi P, Lo vullo S, Guzzo M, et al. Preoperative chemotherapy in advanced resectable OCSCC: long-term results of a randomized phase III trial. Ann Oncol. 2014;25(2):462-6.
3. Driessen CM, De boer JP, Gelderblom H, et al. Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil followed by randomization to two cisplatin-based concomitant chemoradiotherapy schedules in patients with locally advanced head and neck cancer (CONDOR study) (Dutch Head and Neck Society 08-01): A randomized phase II study. Eur J Cancer. 2016;52:77-84.
4. Zhong LP, Zhang CP, Ren GX, et al. Long-term results of a randomized phase III trial of TPF induction chemotherapy followed by surgery and radiation in locally advanced oral squamous cell carcinoma. Oncotarget. 2015;6(21):18707-14.

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