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Trends in Head and Neck Squamous Cell Carcinoma (HNSCC) Clinical Research as Reported in the Asco Proceedings from 1996-2015

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ABSTRACT

Purpose/Objectives: The direction of clinical research can be ascertained by reviewing *ASCO Proceedings* abstracts. We aimed to identify trends in squamous cell-carcinoma of the head and neck **(HNSCC)** as reported in the ASCO annual meetings from 1996-2015 to determine if clinical research findings lead to an improvement in patient survival.

Materials/Methods: All abstracts in the head and neck section of the *ASCO Proceedings* from 1996-2015 were reviewed. Abstracts on locally-advanced, recurrent or metastatic HNSCC were further explored. Descriptive summary information was recorded regarding number of authors, randomization, trial phase, presence of novel drug or combination therapies, timing of chemotherapy, and disease-free and overall survival.

Results: From 1996-2015, there were a total of 2,294 Head and Neck Cancer abstracts. From 1996-2006, 207 abstracts were presented at the ASCO annual meeting. From 2007-2015, 158 abstracts were presented, of which 59 were presented at oral abstract or poster discussion sessions. The average number of authors from 1996-2007 was 8.82, and 10.77 from 2007-2015, with an average number of authors from 1996-2015 of 9.66. 60% of studies from 1996-2006 focused on locally advanced disease, compared to 62% from 2007-2015. From 1996-2006, 27% were randomized studies versus 41% from 2007-2015. From 1996-2006, 57% of abstracts explored concurrent chemo radiotherapy, versus 55% of abstracts from 2006-2015. 50% of abstracts from 1996-2006 investigated a novel drug or novel drug combination, compared to 95% of abstracts from 2007-2015. 6% of abstracts from 1996-2006 demonstrated a statistically significant improvement in survival compared to 7% of abstracts from 2007-2015. Amongst those abstracts from 1996-2006, all were of patients with locally advanced disease, with the majority (7/12) showing a survival benefit of radiation administered with chemotherapy or cetuximab. Amongst those from 2007-2015, 9/11 were in patients with locally advanced disease. Three studies demonstrated the survival benefit of induction chemotherapy, two studies demonstrated the benefit of TPF vs PF, and three studies demonstrated the survival benefit of novel monoclonal antibodies.

Conclusions: Since 1996, the number of clinical trials of HNSCC presented at ASCO annual meeting has increased. There has been a marked increase in the exploration of either novel drugs or novel drug combinations. This has not translated into statistically significant improvements in overall survival because most trials were non-randomized, phase II studies. More randomized clinical trials are needed to build on the successes seen in the treatment of HNSCC. Novel drugs and/or drug combinations will likely lead to paradigm shifts in the treatment of HNSCC.

INTRODUCTION

Worldwide, more than half a million patients receive the diagnosis of squamous-cell carcinoma of the head and neck **(HNSCC)** [1]. There were an estimated 48,330 cases of HNSCC in the United States in 2015, with an estimated 9,570 deaths [2]. Despite a decline in the prevalence of tobacco abuse and in the rates of laryngeal, hypopharyngeal and oral cavity cancers, there is an increase in the overall incidence of head and neck cancers in North America and Europe. This paradoxical trend is attributed in large part to the increased incidence of Human Papilloma Virus **(HPV)** associated malignancies of the oropharynx, particularly over the last 25 years [3]. HPV associated oropharyngeal malignancies have differing demographics, risk factors and prognoses than HPV negative SCCHN [4]. In general, HNC prognosis is determined by anatomic stage and site, with HPV-positivity correlating to significantly improved survival. HPV positive tumors appear to have minimal molecular alterations and therefore favorable outcomes. On the other hand, HPV-negative tumors tend to express frequent molecular and cytogenetic changes which portend less favorable outcomes [1].

New findings over the last several years have led us to have a better understanding of the biologic and molecular features of these tumors. This has resulted in advancements in all approaches of treatment, including radiation therapy, chemotherapy, targeted agents, and surgery.

For example, the implication of epidermal growth factor **(EGF)** over-expression being linked to poor prognosis after treatment of SCCHN has led to trials studying agents directed against blocking epidermal growth factor receptor **(EGFR)**, such as Cetuximab. Vermorken et al. showed that cetuximab plus platinum-flurouracil chemotherapy improved overall survival as first line therapy for patients with recurrent or metastatic SCCHN [5].

Yet, despite these advancements, the estimated death rates for both sexes due to SCCHN has continued to rise over the last several years (i.e. 8,650 deaths in 2015, 9,570 deaths in 2016, and 9,700 in 2017) [2]. The therapeutic implications of this epidemiological shift continue to unfold, and as such, clinical research will be instrumental to determine if the current treatment paradigm is the most appropriate for all subsets of patients with head and neck cancers. In this paper, we have analyzed the *Proceedings of the American Society of Clinical Oncology* ***(ASCO)*** from 1996-2015 to determine whether the presented studies have illustrated a survival advantage. We aim to identify whether clinical research in the field over the past two decades have contributed to the advances in treatment of squamous-cell carcinoma of the head and neck. The *Proceedings of ASCO* represent a cumulative summary of research in the United States and worldwide.

METHODS

We reviewed all abstracts published in the Head and Neck section of the *ASCO proceedings* from 1996-2015. Abstracts were required to have been presented at the ASCO annual meeting in either a poster display or discussion session. We specifically evaluated phase II or phase III prospective trials of different therapeutic modalities, which included chemotherapy, radiation and/or surgery in adult patients with HNSCC. All stages of disease were eligible for inclusion.

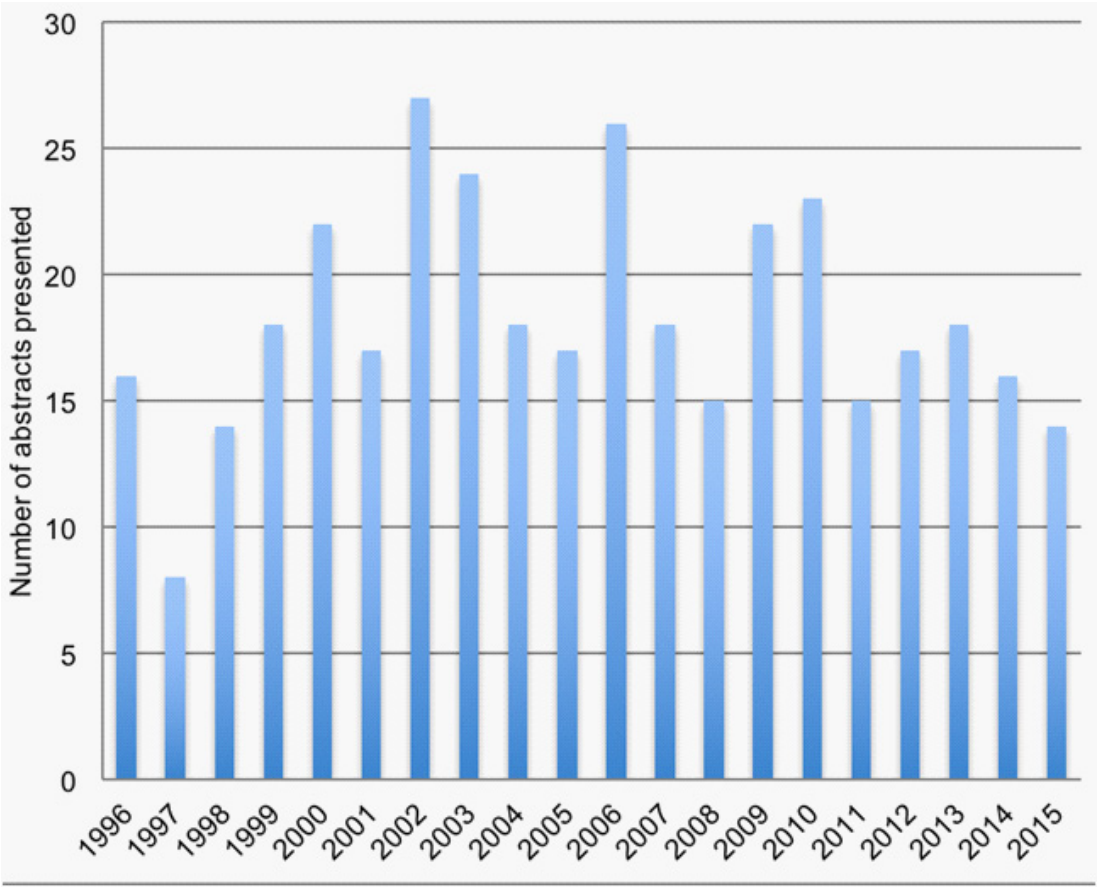
We excluded the following: phase I trials, retrospective studies, epidemiologic studies, quality-of-life studies, or trials of ancillary therapies (e.g. agents to reduce adverse effects of primary therapies). We additionally excluded studies which evaluated patients with any histology other than squamous cell carcinoma, as well as abstracts which focused exclusively on salivary gland carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, bony tumors, or central nervous system tumors. Abstracts that were included in the "publish only" section of the *Proceedings* were not included.

For each abstract meeting the inclusion criteria listed above, the following parameters were recorded: 1. Disease stage (i.e. local, locally advanced, metastatic/recurrent, or a combination of locally advanced and metastatic/recurrent), 2. Trial phase (phase II or phase III), 3. Randomization, 4. Administration of chemotherapy (i.e. adjuvant, neoadjuvant, sole chemotherapy, or concurrent chemotherapy with radiation therapy), 5. Inclusion of a new drug and/or new drug in combination

with standard therapy, 6. Demonstration of statistically significant disease-free survival benefit, 7. Demonstration of statistically significant overall survival benefit.

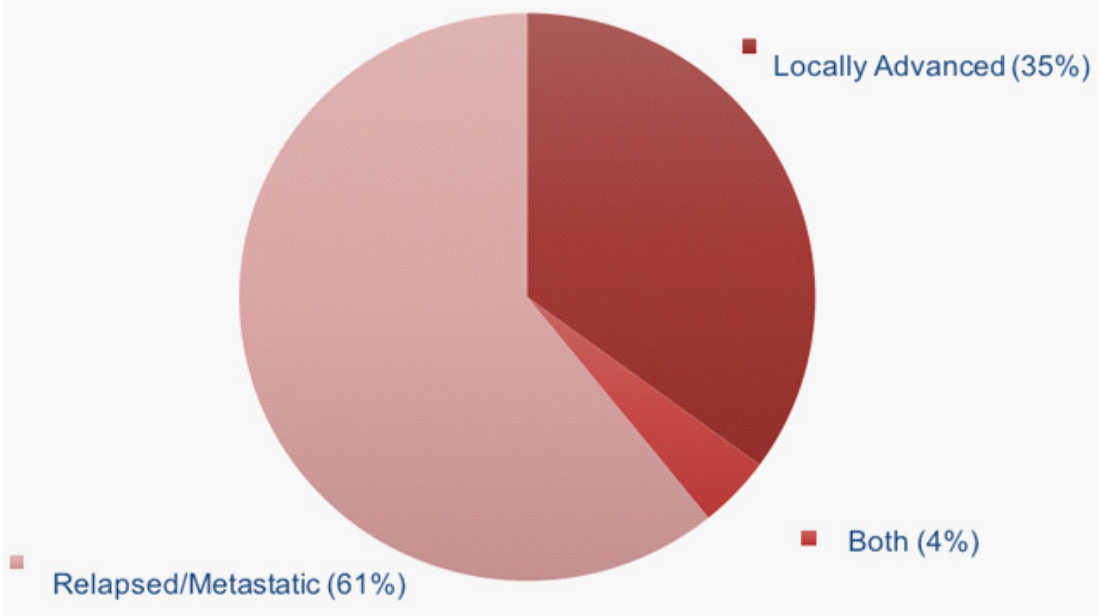
RESULTS

There were a total of 2,294 Head and Neck cancer abstracts between 1996 and 2015 in the *ASCO Proceedings*. Of these, a total of 365 abstracts met the inclusion criteria between 1996 and 2015. The number of phase II and phase III trials presented did not increase as dramatically as the total number of abstracts, and in fact stayed stable, going from 16 in 1996 to 14 in 2015 (*Graph 1*). The average number of authors from 1996-2007 was 8.82, and 10.77 from 2007-2015, with an average number of authors from 1996-2015 of 9.66. A slightly higher proportion of trials from 1996-2015 were performed solely at U.S. institutions (i.e. 69.8% vs. 43.4%). 5.5% of studies were performed by a combination of U.S. and international investigators.



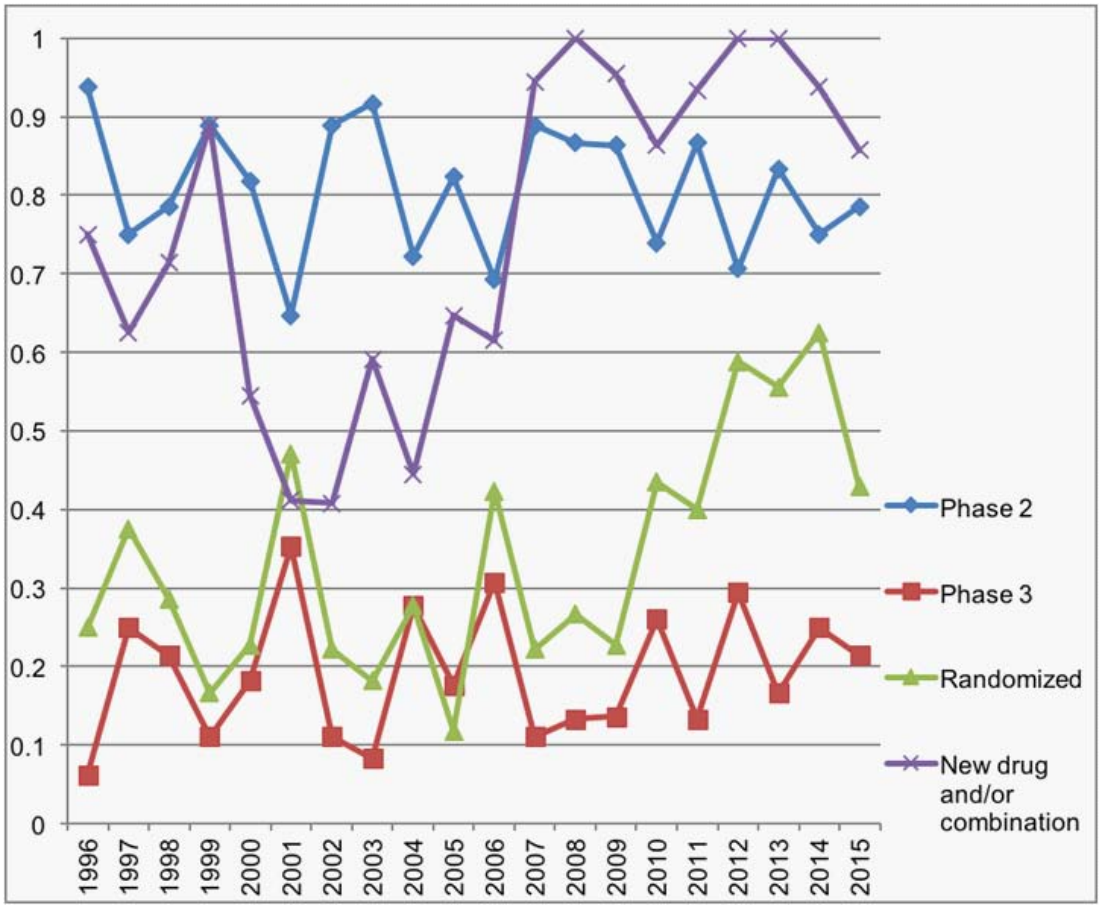
Graph 1: Number of abstracts presented by year.

Graph 2 illustrates the breakdown of disease stage among the presented abstracts. 60.8% of abstracts focused on locally-advanced disease, 35% of abstracts focused on metastatic or recurrent disease, and 4.1% on both locally-advanced and metastatic/recurrent disease.



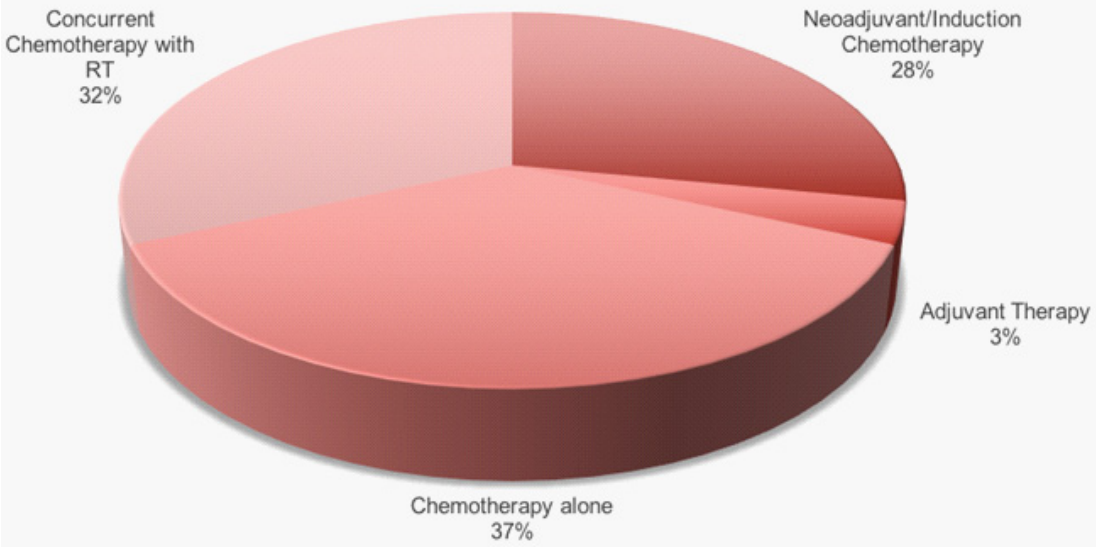
Graph 2: Stages of disease studied amongst presented abstracts.

We also analyzed trends in randomization, phase II vs. phase III study designs, and the evaluation of new drugs and/or new drug combinations *(Graph 3)*. In most years, a minority of studies were randomized and/or had a phase III design. From 1996-2006, 27% were randomized studies versus 41% from 2007-2015.



Graph 3: Trends in randomization, study design, and study of novel drugs.

Most abstracts presented data on new agents or drug combinations. 50% of abstracts from 1996-2006 investigated a novel drug or novel drug combination, compared to 95% of abstracts from 2007-2015. The proportion of abstracts over the 19-year period studying induction or adjuvant chemotherapy, chemotherapy alone, and concurrent chemotherapy with radiation therapy were similar. Adjuvant chemotherapy was studied less often *(Graph 4)*.



Graph 4: Proportions of therapies studied between 1996-2015.

A minority of studies have shown either a benefit in overall survival or disease-free survival. Of the 365 abstracts presented, 6% of abstracts from 1996-2006 demonstrated a statistically significant improvement in survival, compared to 7% of abstracts from 2007-2015. Amongst those abstracts from 1996-2006, all were of patients with locally advanced disease, with the majority (7/12) showing a survival benefit of radiation administered with chemotherapy or cetuximab. Amongst those from 2007-2015, 9/11 were in patients with locally-advanced disease. Three studies demonstrated the survival benefit of induction chemotherapy, two studies demonstrated the benefit of docetaxel/cisplatin/fluorouracil (TPF) vs.cisplatin/fluorouracil (PF), and three studies demonstrated the survival benefit of novel monoclonal antibodies (e.g. Nimotuzumab) of the total number of abstracts which demonstrated an overall survival benefit from 1996-2015, 56.6% reported a novel drug or novel drug combination.

Twenty-seven abstracts showed a statistically significant benefit in disease-free survival. Thirteen of these studies also showed a significant overall survival benefit. A major trend of these studies, as with the trials showing an overall survival benefit, was a benefit seen with concurrent chemo radiotherapy as opposed to radiation therapy alone. A majority of these trials focused on locally-advanced disease with the exception of five trials which studied metastatic/recurrent HNSCC. The abstracts which included metastatic/recurrent HNSCC assessed novel monoclonal antibodies alone or in combination (i.e. zalemtumumab, cetuximab, panitumumab) and one of these compared metronomic therapy with single-agent cisplatin.

DISCUSSION

Only a small proportion of abstracts detailing phase II and phase III HNSCC clinical trials have shown a benefit in either overall survival or disease-free survival. The main therapeutic advance these studies have uncovered is the benefit of concurrent chemo radiotherapy in locally-advanced disease. As evidenced in clinical practice now, combination therapy (hyper-fractionated irradiation plus concurrent chemotherapy) has been shown to be more efficacious and not less toxic than radiotherapy alone in locally-advanced disease [6].

Despite only a small proportion of abstracts showing clear survival benefits, investigation into novel drugs and/or novel drugs in combination with standard therapy has been vigorous over the last two decades. Cetuximab and the addition of docetaxel to platinum and 5-fluorouracil have been the main new therapeutic breakthroughs. The addition of cetuximab to platinum-based chemotherapy with 5-fluorouracil has been shown to significantly improve median overall survival as well as prolong median progression-free survival in recurrent or metastatic HNSCC [5]. These abstracts have also addressed another novel drug, nivolumab, which has been shown recently to increase overall survival when compared to standard systemic therapy with methotrexate, docetaxel, and cetuximab in patients with recurrent or metastatic HNSCC who had progressed within six months after chemotherapy [7].

Many factors may account for the small proportion of abstracts illustrating clinically significant results. Randomized phase III trials are the most powerful in showing a therapeutic benefit. However, the majority of studies evaluated in the *ASCO Proceedings* were non-randomized and not of phase III design. Phase III studies only comprised 18.9% of abstracts from 1996-2015 [8-10]. While randomized phase III studies require a significant amount of time to complete patient accrual and follow-up, more of these studies will be needed to show the benefits of novel therapies. Additionally, most of the studies presented in the *ASCO Proceedings* had a relatively small sample size. Studies that potentially could have shown a benefit may have suffered from a lack of power due to inadequate patient enrollment [10-12].

CONCLUSIONS

Since 1996, the number of clinical trials of HNSCC presented at the *ASCO* annual meeting has increased. Particularly, there has been a marked increase in the exploration of either novel drugs or novel drug combinations. This has not yet translated into studies showing statistically significant improvements in overall survival. This is likely because most of the presented trials were non-randomized phase II studies. More randomized phase III clinical trials will be needed to build on the successes seen in the treatment of HNSCC. Novel drugs, particularly monoclonal antibodies such as nivolumab and cetuximab, are playing a significant role in treatment of metastatic or recurrent HNSCC. Given the advances in knowledge regarding the molecular mechanisms of the tumor as well as the increased prevalence of HPV-associated HNSCC, it will also be interesting to note paradigm shifts in the treatment of HPV-associated HNSCC in the future.

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