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Treatment trends in oropharyngeal carcinoma: Surgical technology meets the epidemic

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ABSTRACT

Objective: To characterize temporal trends in treatment patterns for oropharyngeal carcinoma, and to evaluate the emerging role of surgical therapy in the era of transoral robotic surgery (TORS).
Methods: Patients with oropharynx cancer between 2004 and 2016 identified using the National Cancer Database. Demographics and primary treatment modalities were obtained. Treatment was classified as surgery alone, surgery with radiation/chemotherapy, or primary radiation/chemotherapy. Annual distribution of cases treated by the various modalities was tabulated by site and early (I/II) versus late (III/IV) stage disease (AJCC 7th edition). The "TORS era" was defined as beginning in 2010.
Results: 149,534 patients were identified. The majority (56.8%) were treated with radiation ± chemotherapy. 53,069 patients had surgery as part of treatment, 72.6% (N = 38,533) of which received adjuvant therapy. 5293 TORS procedures were performed between 2010 and 2016 with trends away from open and other endoscopic procedures. Despite a 31.0% increase in the number of cases treated surgically from before TORS (2009) to 2016, the percentage of cases treated surgically decreased from 35.0% to 32.7%, with a 44.2% increase in non-surgical therapy. Increases in the percentage of patients treated surgically were observed for base of tongue tumors (24.3–25.2%) and early stage disease (59.9–62.2%).
Conclusion: Despite the increase in the overall number of patients with oropharynx cancer, the percentages of patients treated surgically remains relatively stable. Notable increases were observed for base of tongue tumors and early stage disease.

Introduction

The rising incidence of oropharyngeal squamous cell carcinoma (OPSCC), in the setting of the human papilloma virus (HPV) epidemic, is well described. In 2015 alone, 16,420 cases were diagnosed in the United States [1,2]. The number of cases is expected to double by 2030 [3]. HPV-related disease seems to affect a much younger, healthier population, with improved therapeutic outcomes relative to its smoking-related, HPV (–) counterparts [4–6].

Traditional open surgical resection of OPSCC have been associated with significant morbidity [7]. External incisions, mandibulotomy, pharyngotomy, tracheotomy, and almost obligate flap reconstruction result in substantial disfigurement and swallowing dysfunction. Not surprisingly, there has been greater enthusiasm for non-surgical therapy in these patients. Radiotherapy or chemoradiotherapy had become the mainstay, with emphasis on organ preservation [8]. Although effective, chemoradiation has its own late toxic effects, most commonly pharyngeal dysfunction, xerostomia, and stricture [9,10].

Across a similar timeframe to the rise in the incidence of OPSCC, however, advances in surgical techniques were occurring. Refinement of transoral laser microsurgery and the advent of transoral robotic surgery (TORS), allowed the re-introduction of surgery into the management paradigm. These minimally invasive approaches have been shown to be oncologically effective, with evidence of improved functional outcomes and quality of life. [11] Similarly, intensity modulated radiation therapy has significantly improved the therapeutic ratio of radiotherapy [4,11,12]. The combination of minimally invasive surgery with IMRT provides the opportunity for significant de-intensification of therapy in these patients.

With its Food and Drug Administration (FDA) approval in December

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2009, TORS using the daVinci surgical system has gained increasing popularity in the management of OPSCC. The procedure is offered at nearly every academic medical center in the United States. The availability of TORS is felt to represent a paradigm shift in the management of OPSCC, with a movement away from primary chemoradiation. The objective of this study is to examine trends in therapy over time using the National Cancer Database (NCDB). The hypothesis is that following the introduction of TORS into the therapeutic arsenal, a significant shift towards surgical therapy should be observed.

Methods

Data originated from the NCDB from 2004 to 2016. The NCDB is a nationwide clinical surveillance resource data set that includes approximately 70% of all newly diagnosed malignancies. It includes all cancer cases treated at American College of Surgeons Commission on Cancer (CoC) accredited hospitals in the United States. It is well described elsewhere [13].

Patients were included with a diagnosis of squamous cell carcinoma of the oropharynx. Oropharyngeal primaries were defined using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) site codes. This includes C09.0 through C09.9 (tonsil), C01.9 (base of tongue), C10.2, C10.3, C10.8, C10.9 (oropharynx), and C14.0, C14.2 (pharynx NOS, excluding hypopharynx/nasopharynx). Only adult patients (age 20 +) were included. Nonsquamous cell histologies or cases identified through autopsy were excluded. Demographic data included age at diagnosis, gender, race, and urban/rural status. Urban/rural status was based on the U.S. Department of Agriculture's Rural-Urban Continuum Codes (urban 1–3, rural 4–9). (ref: Service USDoAER. Rural-Urban Continuum Codes. https://www.ers.usda.gov/data-products/rural–urban-continuum-codes/documentation/. Accessed December 1, 2018.) HPV status was included in the data from 2010 forward. Patients were staged using the American Joint Committee on Cancer (AJCC) 7th edition to best reflect the staging system utilized during the treatment period [14]. Treatment was categorized as surgery alone, surgery with adjuvant radiotherapy ± chemotherapy, no treatment, or unknown. Patients were categorized by year of diagnosis, with both raw numerical data and percentage of treatment by year presented. Type of surgery for primary site disease was categorized using the NCDB variable for "surgical approach". Patients having surgery was classified as robotic or endoscopic, both with and without conversion to an open procedure, as well as open approaches.

Descriptive analysis was performed to examine the demographics and clinical factors by the five sub-oropharyngeal cancer sites. Raw number and distributions of treatment over years were provided and a chi-square test was performed. Various linear regressions were fitted with year as the single covariate to examine the trends over time. Analyses were two-sided with a p-value ≤ 0.05 used to identify statistical significance. All analyses were performed using SAS Statistical Software version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

149,534 patients with OPSCC were identified in the database. As seen in Fig. 1, the annual number of new cases continues to increase steadily, from 7840 in 2004 to 15,218 in 2016. This represents approximately a 94% increase in cases over the study period. Demographics are listed in Table 1. Patients are predominantly white, male, and between the ages of 50 and 64. The majority of tumors were classified as being of tonsil (45.1%) and base of tongue (39.3%) origin, with the remainder classified as oropharynx (11.6%) or pharynx (not hypopharynx or nasopharynx, 4.0%). HPV status was not included in the database before 2010, leaving 55,270 patients with no data. Of the 94,264 patients diagnosed between 2010 and 2016, 39,385, or 41.8%, still had HPV status classified as unknown. 54,879 patients between 2010 and 2016 had known HPV status, 70.7% were HPV positive. Of

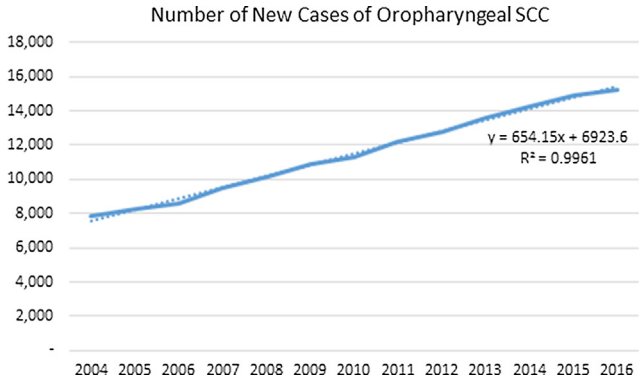

Fig. 1. Cases of squamous cell carcinoma of the oropharynx by year.

the patients with known staging data, 76.4% were classified as AJCC stage III/IV disease, the majority of patients were AJCC stage IVa (41.9%). This was primarily a function of advanced nodal disease. 42.7% of patients were staged as N2a or greater. This was in spite of the fact that 71.3% of patients were classified as having T1/T2 primary tumors. These findings are relatively consistent with the known pathophysiology of HPV-related OPSCC. Only 2.5% of patients presented with distant metastatic disease (TNM data not shown).

53,069 patients had surgery as part of their treatment. 14,536 were treated with surgery alone, while the remaining 38,533 received some form of adjuvant therapy in addition to surgery as their primary treatment. Thus, surgery was utilized in 35.5% of all patients with known treatment. Radiation therapy, with or without chemotherapy was used as part of therapy in 123,439 patients, with 84,906 being treated with radiation as the primary treatment modality. 97,686 received some form of chemotherapy, 65,103 receiving single agent therapy, and 32,583 receiving multi-agent treatment. The vast majority of patients were treated with primary radiation, with or without chemotherapy. The exception to this is tonsil primaries, where surgical therapy, with or without adjuvant therapy (47.7%) was about the same as radiation ± chemotherapy (47.5%).

Annual trends in treatment are shown in Table 2. Both overall numbers and percentages are presented. The raw number of cases treated with all modalities appears to increase steadily over the study period, which would appear to be a function of the increasing prevalence of the disease. With the FDA approval of TORS in December 2009, surgical cases from 2010 to 2016 were considered to be in the "TORS era". Overall cases with surgery as part of therapy increased from 3815 in 2009 to 4989 in 2016, a 30.8% increase. However, the number of cases per year increased over that same timeframe from 10,887 in 2009 to 15,218 in 2016, a 39.8% increase. Thus, the *proportion* of patients treated at least in part with surgery actually decreased slightly from 35.0% in 2009 to 32.7% in 2016. Primary radiation ± chemotherapy over that time increased from 6244 cases to 9005 cases, a 44.2% increase. These findings are graphically represented in Fig. 2. For tonsil primaries, there was a 26.3% increase in the overall number of surgical cases, but the percentage of cases treated surgically decreased from 47.8% in 2009 to 43.1% in 2016. There was, however, a 46.1% increase in the number of base of tongue cancers with surgery as part of treatment. The number of cases increased from 989 in 2009 to 1445 in 2016, with a slight increase in the percentage of cases treated surgically from 24.3% to 24.4%.

Treatment trends for early (I/II) versus late (III/IV) stage disease are demonstrated in Figs. 3 and 4. As seen in Fig. 3, early stage disease demonstrates a longstanding trend toward surgical therapy, unlike the majority of the cohort. However, there is a definite trend toward the increased use of surgical therapy in the "TORS era". Overall, cases with surgery as part of treatment increased from 910 cases (59.2%) in 2009 to 990 cases (62.6%) in 2016. The percentage of cases treated with surgery alone increased from 30.7% (N = 471) in 2009 to 40.0%

Table 1
Demographic data.

		Tonsil	BOT	Oropharynx	Pharynx	Total
N		67,386	58,708	17,388	6,052	149,534
Gender						
	Male	54,848 (81.4%)	47,838 (81.5%)	13,246 (76.2%)	4514 (74.6%)	120,446 (80.5%)
	Female	12,538 (18.6%)	10,870 (18.5%)	4142 (23.8%)	1538 (25.4%)	29,088 (19.5%)
Race						
	Caucasian	59,772 (88.7%)	52,584 (89.6%)	14,489 (83.3%)	5148 (85.1%)	131,993 (88.3%)
	African American	5627 (8.4%)	4460 (7.6%)	2447 (14.1%)	698 (11.5%)	13,232 (8.8%)
	Other	1290 (1.9%)	1072 (1.8%)	298 (1.7%)	138 (2.1%)	2798 (1.9%)
	Unknown	697 (1.0%)	592 (1.0%)	154 (0.9%)	68 (1.1%)	1511 (1.0%)
Age						
	20–49	12,039 (17.9%)	6630 (11.3%)	1968 (11.3%)	610 (10.1%)	21,247 (14.2%)
	50–64	37,915 (56.3%)	29,874 (50.9%)	8708 (50.1%)	2778 (45.9%)	79,275 (53.0%)
	65–74	12,598 (18.7%)	14,908 (25.4%)	4484 (25.8%)	1618 (26.7%)	33,608 (22.5%)
	> 75	4834 (7.2%)	7296 (12.4%)	2228 (12.8%)	1046 (17.3%)	15,404 (10.3%)
HPV status						
2004–2009	(unknown)	24,757	21,710	6588	2215	55,270
2010–2016	Positive	20,778 (48.7%)	14,652 (39.6%)	2690 (24.9%)	657 (17.1%)	38,777 (41.1%)
	Negative	6455 (15.1%)	6285 (17.0%)	2503 (24.9%)	859 (22.4%)	16,102 (17.1%)
	Unknown	15,396 (36.1%)	16,061 (43.4%)	5607 (51.9%)	2321 (60.5%)	39,385 (41.8%)
AJCC stage (7th edition)						
	0	517 (0.8%)	448 (0.8%)	202 (1.2%)	1 (0.02%)	1168 (0.8%)
	I	3597 (5.3%)	3473 (5.9%)	1183 (6.8%)	1 (0.02%)	8254 (0.5%)
	II	5587 (8.3%)	4167 (7.1%)	1501 (8.6%)	0	11,255 (7.5%)
	III	12,902 (19.2%)	9728 (16.6%)	2763 (15.9%)	5 (0.08%)	25,398 (17.0%)
	IV	41,120 (61.0%)	37,459 (63.8%)	10,231 (58.5%)	12 (0.2%)	88,822 (59.4%)
	Unknown	3663 (5.4%)	3433 (5.9%)	1508 (8.7%)	6033 (99.7%)	14,647 (9.8%)

BOT: Base of Tongue.
HPV: Human Papillomavirus.
AJCC: American Joint Commission on Cancer.

(N = 632) in 2016. Fig. 4 demonstrates that while there is an increasing trend in the use of surgery for late stage disease, it is far outpaced by non-surgical therapy. It is important to note that only 19,509 patients with known stage were classified as early stage disease, compared with 114,219 late stage patients, further emphasizing the magnitude of the increase in non-surgical management.

Of the 53,069 patients between 2010 and 2016 that had surgery as part of their primary treatment, 32,902 had surgery for disease of the primary site as classified in the database by surgical approach. The remaining 7282 were classified as having no surgical procedure of the primary site. Presumably, these patients had some form of neck dissection followed by adjuvant therapy. Annual distribution of primary site surgery is shown in Fig. 5. Overall, there were 5375 TORS procedures performed between 2010 and 2016, 82 of which were classified as converted to open (1.5%). Thus, 5293 procedures were completed with TORS. Over the same time, there were 4677 endoscopic procedures performed, 213 converted to open (4.5%), and 4464 successfully performed endoscopically. The difference in rate of conversion to an open procedure between approaches is statistically significant ($p < 0.00001$). 15.568 open procedures were performed. As can be seen in Fig. 5, the number of TORS cases increased annually, peaking at 1045 successfully completed TORS procedures in 2016, while the number of endoscopic procedures leveled off after 2014. While open procedures made up the majority of primary site surgery, their frequency decreased from a peak of 2291 procedures in 2013 to 2155 in 2016.

Discussion

In recent years, more than any other head and neck cancer, OPSCC has undergone a significant paradigm shift in terms of etiology, management, and prognosis [8]. Despite declines in smoking and alcohol

Table 2
Treatment by year for all tumor sites by both raw number and percentage of patients treated annually by each modality. Raw numbers and percentages are listed separately.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Number treated														
No treatment	541	587	572	598	656	722	761	814	866	826	957	992	1006	9898
Surgery alone	814	794	795	853	929	1061	1054	1221	1307	1344	1387	1452	1525	14,536
Surgery + XRT/chemo	2242	2289	2372	2613	2651	2754	3006	3207	3270	3548	3558	3559	3464	38,533
XRT/chemo	4172	4491	4789	5339	5836	6244	6374	6784	7180	7726	8210	8756	9005	84,906
Unknown	71	95	93	97	94	106	103	158	130	154	167	175	218	1661
Total	7840	8256	8621	9500	10,166	10,887	11,298	12,184	12,573	13,598	14,279	14,934	15,218	149,534
Percent treated														
No treatment	6.9	7.1	6.6	6.3	6.5	6.6	6.7	6.7	6.8	6.1	6.7	6.6	6.6	6.6
Surgery alone	10.4	9.6	9.2	9.0	9.1	9.8	9.3	10.0	10.3	9.9	9.7	9.7	10.0	9.7
Surgery + XRT/chemo	28.6	27.7	27.5	27.5	26.1	25.3	26.6	26.3	25.6	26.1	24.9	23.8	22.8	25.8
XRT/chemo	53.2	54.4	55.5	56.2	57.4	57.4	56.4	55.7	56.3	56.8	57.5	58.6	59.2	56.8
Unknown	0.9	1.1	1.1	1.0	0.9	1.0	0.9	1.3	1.0	1.1	1.2	1.2	1.4	1.1

XRT: Radiation Therapy.
Chemo: Chemotherapy.

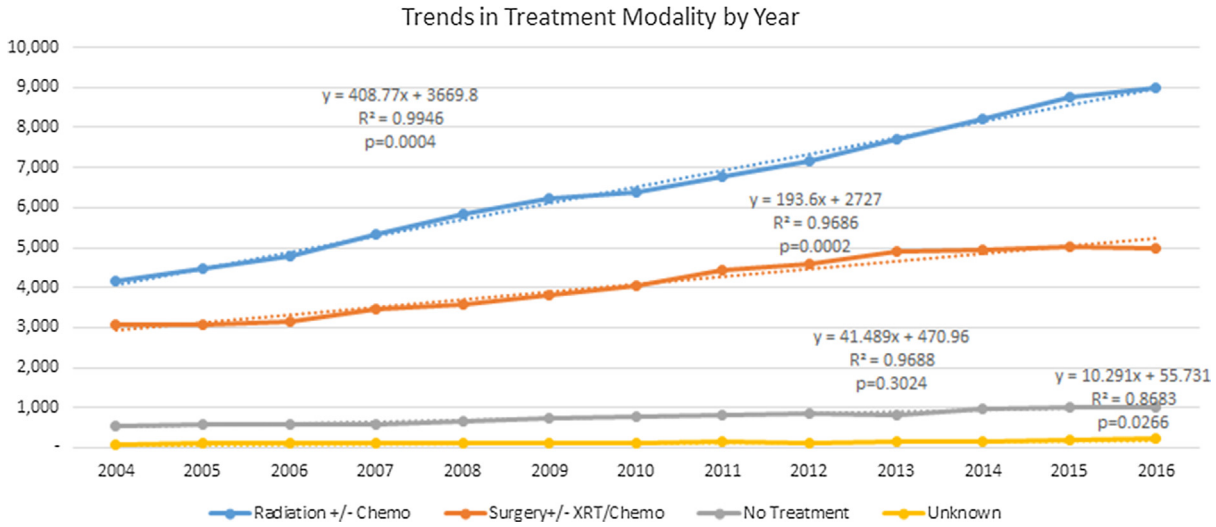

Fig. 2. Trends in treatment modality by year. Patients treated with radiation, with or without chemotherapy compared to patients treated with surgery, with or without adjuvant radiation and/or chemotherapy.

consumption, the incidence of OPSCC continues to rise due to the impact of human papilloma virus (HPV) on its carcinogenesis. Although historically, open surgical resection with indicated adjuvant therapy was considered the treatment of choice for tumors of the oropharynx, the impact of these procedures on speech and swallowing led to enthusiasm for the application of non-surgical, organ preservation therapy as a preferred modality in these patients [15–17].

Generally speaking, there are three standard treatment options for OPSCC: (1) surgery followed by adjuvant therapy based on pathologic assessment of risk factors, (2) concurrent radiotherapy and chemotherapy (i.e., chemoradiation), and (3) neoadjuvant chemotherapy followed by definitive chemoradiation [18]. Preferred therapy is often a function of institutional preference. These treatments result in excellent disease control and survival. However, they are not without substantial toxicity [10,19–22]. Concerns for "overtreatment" of HPV-associated OPSCC have led to efforts to reduce the intensity of treatment. As the reduction of intensity of one modality is often offset by the increase in another, renewed interest in surgical management has occurred [23]. The minimally invasive techniques of transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) are regularly utilized as a primary therapeutic option [24–30]. With favorable oncologic outcomes and reduced treatment toxicity, these approaches appear to be gaining favor in the literature [31,32].

The results of this study, however, reveals two findings contrary to these sentiments. First, although there appears to be a decrease in their absolute numbers, the most common surgical approach for primary site oropharyngeal carcinoma remains the open procedure. Second, non-surgical therapy, specifically radiation with or without chemotherapy, remains the mainstay of treatment. Although the raw number of cases treated surgically continues to increase over time, it is outdistanced by the number of new cases of OPSCC, and the balance of these cases are being treated non-surgically. Of the 15,218 new cases of OPSCC in 2016, only 1045 (6.8%) were successfully treated with TORS. Only 668, or 4.6%, were treated endoscopicly, presumably a measure of transoral laser microsurgery. Conversely 2110, or 14.5%, were treated with an open procedure.

There are several potential explanations for these observations. First, adoption of primary surgical approaches in the management of

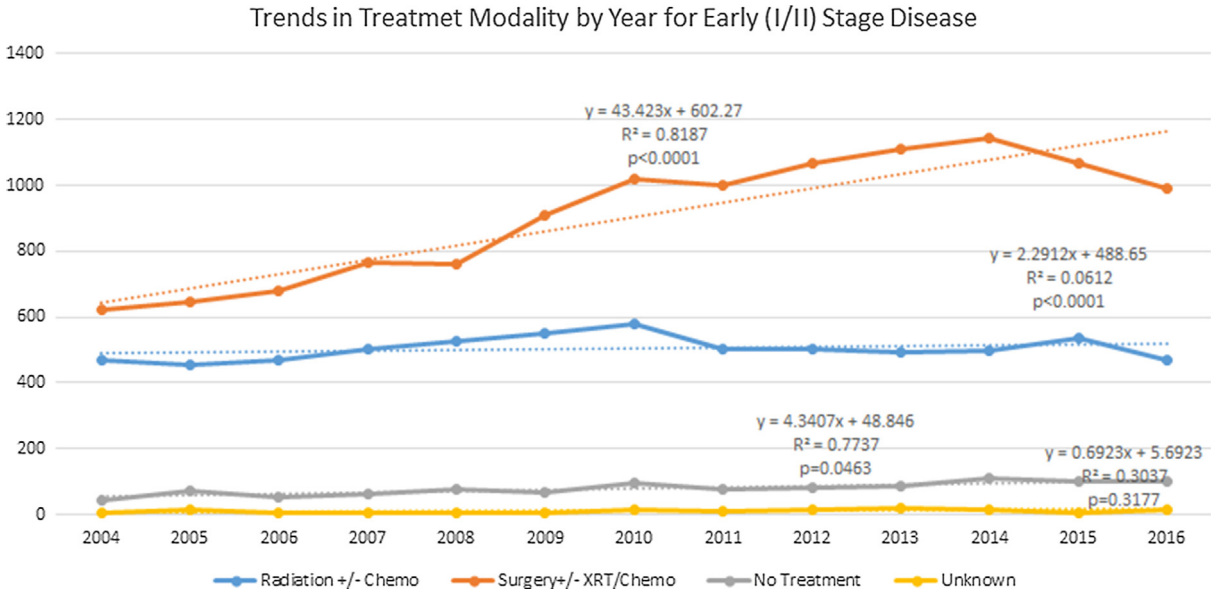

Fig. 3. Trends in treatment for early stage (I/II) disease. Patients treated with radiation, with or without chemotherapy compared to patients treated with surgery, with or without adjuvant radiation and/or chemotherapy.

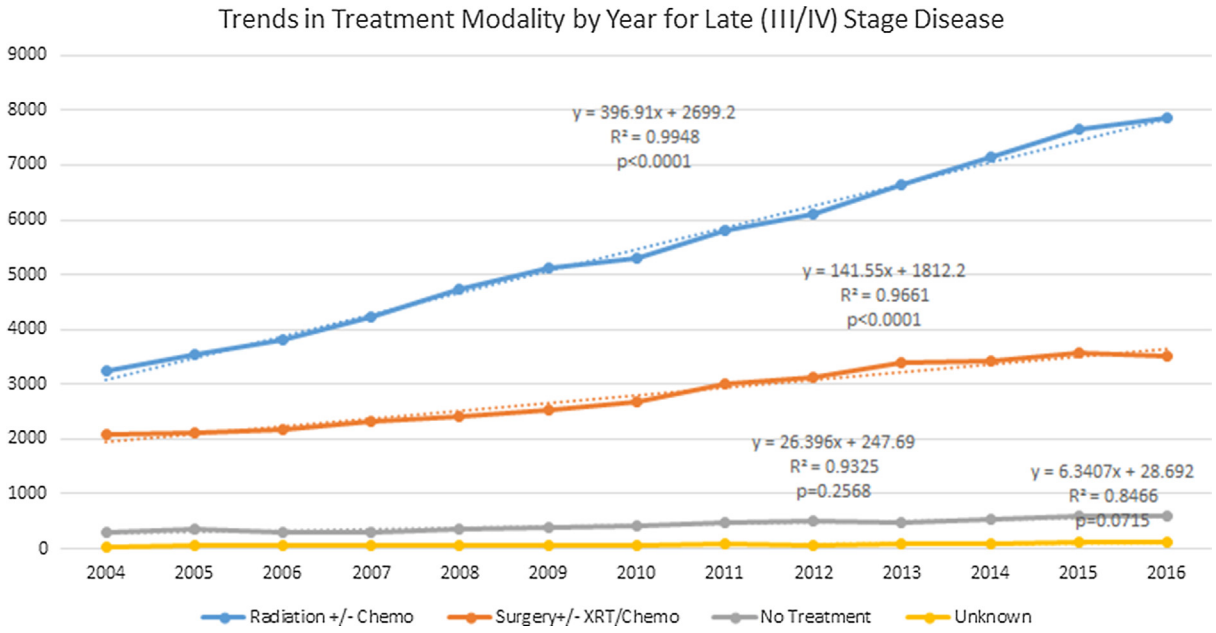

Fig. 4. Trends in treatment for late stage (III/IV) disease. Patients treated with radiation, with or without chemotherapy compared to patients treated with surgery, with or without adjuvant radiation and/or chemotherapy.

oropharyngeal cancer may not be universally accepted. Controversy regarding optimal treatment strategies for this disease undoubtedly remain. While many centers have adopted a strong preference for surgical management of OPSCC, a continued nationwide preference for non-surgical therapy may still exist. Similar observations noting an increased use of radiation for OPSCC over time have been presented in prior studies using SEER data [33]. Transoral surgical approaches of any type tend to be centralized in academic or at least larger cancer facilities. A remaining tendency toward non-surgical therapy is likely to exist in smaller, community institutions. Furthermore, lack of access, whether from lack of awareness or lack of means to seek the care of minimally invasive surgeons, may further hamper these trends. It is unlikely that the current number of surgeons are oversaturated with cases, or "too busy". Rather, it is more likely that cases eligible for surgical management are not getting to the proper facilities, or patients are not being made aware of this option.

Additionally, open surgical procedure still appear to remain the more prevalent approach of choice for management of primary site disease. Several possibilities exist for this observation. The first is the potential under-appreciation of advanced primary site disease, which may be beyond the capabilities of minimally invasive techniques. Open surgical procedures were observed to be more common in patients with late stage disease. As patients were staged using the 7th Edition of the AJCC manual, it was difficult to determine which patients had open procedures for advanced primary site disease versus patients with advanced stage for neck disease alone. Primary site surgery, however, is generally based on T stage, which differs little between the 7th and 8th edition. It is unlikely that small primary tumors, many of which can be addressed transorally without robotic or laser microsurgical techniques, are being managed with large, open procedures. The type of open procedure, such as mandibulotomy or lateral pharyngotomy, is not specified in the data. Therefore it is possible that patients with planned neck dissection are still approached trancervically, particularly if flap reconstruction is anticipated, and are thus classified as open procedures. Whether transoral surgery performed neither endoscopically or robotically is classified as an "open" procedure is unclear and potentially a shortcoming of the database. Given the availability of minimally invasive surgery at nearly all academic and major cancer institutions, a preference for open surgery due to lack of availability is unlikely. The trends do suggest a decrease in the number of open procedures. While

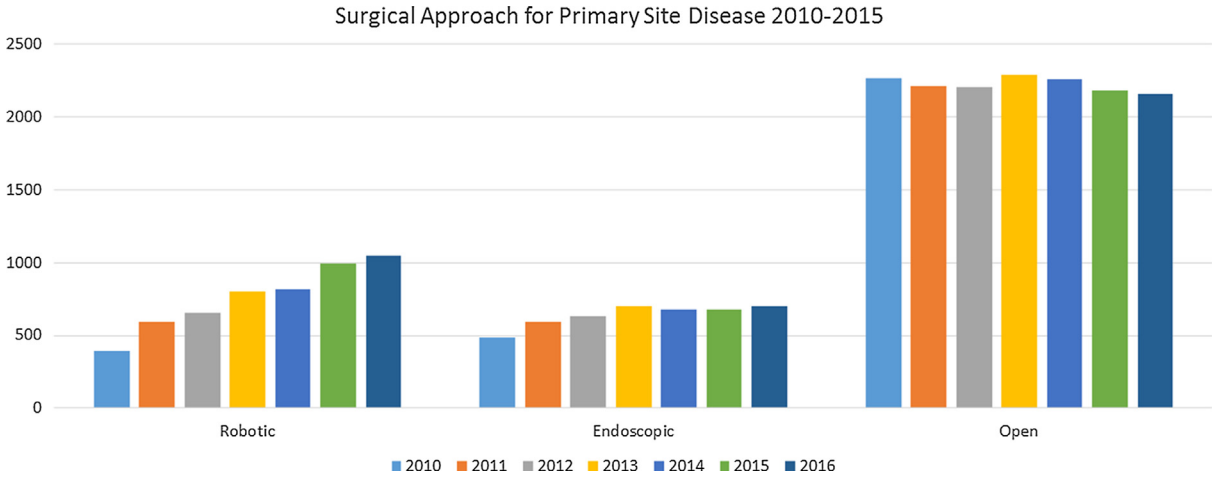

Fig. 5. Trends in surgical approach for primary site disease from 2010 to 2016.

this appears to be occurring in the presence of an observed increase in robotic procedures, it is important to note the overwhelming increase in the number of patients treated non-surgically over this period.

Similar reductions in primary site surgery classified as endoscopic are also observed. It is presumed that this classification is meant to represent cases treated with transoral laser microsurgery. However, the particular nomenclature is admittedly misleading. It is hypothesized that this is meant to include cases that were performed using microscopic or endoscopic techniques without specifically using a laser, but undoubtedly there is bound to be some degree of misclassification. While the number of cases with this classification appears to peak in 2013 followed by a reduction in the number of annual cases, it is unclear if this represents a shift towards robotics or simply a further reflection of the overwhelming trend toward non-surgical therapy. As a result, it is difficult to make any significant commentary on trends in transoral laser microsurgery. Classification of cases as “robotic” however, is less likely to be an issue as these procedures are generally institutionally tracked.

An unexpected, incidental finding was the percentage of robotic cases necessitating conversion to open procedures. As a “newer” technology, a learning curve would be expected, theoretically resulting in a higher rate of conversion to more “conventional” approaches. Endoscopic transoral approaches are more established procedures, with an anticipated level of expertise in experienced hands. The rates of conversion of both robotic procedures end endoscopic procedure to open surgery remained relatively consistent over the five-year period. Whether this is a testament to the efficacy of TORS, or simply a reflection of its more conservative use in its nascence, is unclear.

It is important to emphasize that this study is not a testament to the effect of treatment approach on cancer control or survival. Numerous studies using these data from the NCDB for that purpose have been performed, with mixed results [34–42]. Increased rates of surgery for T1/T2 tumors over similar time periods have been observed. However, the proportion relative to the number of overall cases and the relative overall increase in non-surgical therapy has not previously been discussed [43]. The objective of this study was to evaluate the actual landscape of therapy in the setting of increased awareness of the role of surgery, particularly minimally invasive approaches such as TORS and TLM. The results suggest that despite the increased awareness of the role of these procedures in the management of OPSCC, their place remains a small one, which is actually decreasing relative to the increasing incidence of disease. Based on observed trends, it is likely that the volume of TORS will continue to increase as further data becomes available. However, as observed in this study, these cases represent a small fraction of the overall cases. Increased awareness of surgical options, increased access to surgical therapy, and ultimately increased evidence of the efficacy of surgery in the de-escalation of non-surgical adjuvants, will all likely play a role in the alteration of these trends.

Conclusion

Despite the increase in the overall number of patients with oropharynx cancer, the percentages of patients treated surgically remains relatively stable, resulting in an observed decrease in the proportion of patients with surgery as part of their primary treatment regimen. Prevalence of robotic surgery is increasing relative to alternative open or endoscopic approaches, but makes up a minority of treated cases. Primary surgery, with or without adjuvant therapy, is primarily utilized for early stage disease.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.08.007.

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