Larynx and hypopharynx cancer

Educated choices in treatment and rehabilitation

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General discussion and future perspectives
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Over the past decades, the field of advanced larynx and hypopharynx cancer has witnessed several important changes in terms of treatment, survival and rehabilitation. Since the publication of the landmark randomized controlled trials (RCTs) evaluating organ preservation therapy in advanced larynx and hypopharynx cancer, an increasing number of patients were treated with organ preservation protocols instead of total laryngectomy (TL). For larynx cancer, the first (Veterans Administration; VA) trial in 1991, demonstrated an equal overall survival (OS) rate of 68% at 2 years. The subsequent RTOG 91-11 trial demonstrated the superiority of concurrent chemoradiotherapy over induction chemoradiotherapy or single modality radiotherapy. In 1996, Lefebvre et al. demonstrated the safety and efficacy of induction chemotherapy followed by radiotherapy in hypopharynx cancer. Several subsequent RCTs have focused on the type of chemotherapy, the use of cetuximab or the effect on larynx preservation, but none of these studies have however specifically compared concurrent CRT with TL in hypopharynx cancer patients.

One and a half decade after the VA trial, in 2006, Hoffman et al. raised concerns about a decreasing overall survival rate for advanced larynx cancer, which seemed to coincide with the increasing application of organ preservation protocols. To assess whether such trends could be witnessed in the Netherlands as well, Timmermans et al. performed a population-based study evaluating all patients treated for T3-T4 squamous cell carcinoma (SCC) of the larynx between 1991-2010. This study did not show a decrease in OS rates over time in the Netherlands, despite the fact that similar to the results from Hoffman et al., also here a clear trend towards more organ preservation strategies was noted. However, patients with T4 larynx cancer showed better OS rates when treated with TL compared to CRT, something that in hindsight also was observed in the first VA study.

Because of the close anatomical proximity of the larynx to the hypopharynx, treatment strategies for larynx cancer are often one-to-one translated to patients with hypopharynx cancer. The first RCT demonstrating the safety of chemoradiotherapy in hypopharynx cancer was published in 1996, but around the world, many patients with hypopharynx cancer were already treated with CRT years before this publication. We were interested in evaluating whether similar trends in treatment for hypopharynx cancer could be witnessed in The Netherlands, and what the effect of this possible trend would be on survival. Similar to the national larynx cancer study, we performed a population-based study evaluating the trends in treatment, incidence and survival of hypopharynx cancer, described in chapter 2. We combined a national database from the Netherlands Cancer Registry (NCR) with the national pathology database (PALGA), and evaluated all patients treated for T1-T4 SCC of the hypopharynx in the period 1991-2010. Incidence and mortality rates were assessed for the period 1989-2013. We found that the incidence of hypopharynx cancer in the overall population showed an initial increase from 1989 to 1997, but has been slowly decreasing since then. Among female patients, who accounted for 18% of the total hypopharynx cancer population, a significant increase was observed however, with an annual percentage change (APC) of 1.7% over the years 1989-2013. Possibly, this latter finding is related to the increased smoking behavior of women; the proportion of smokers among women increased from 29% in 1958, to its highest level of 42% in 1970. Since then, it has decreased again to 26% in 2010. The smoking behavior of males, on the other hand, continued to decline drastically; the proportions of smokers among men was 90% in 1958 and 28% in 2010. This could explain the decreasing incidence of hypopharynx cancer among males since 1997.

Similar to trends observed regarding the treatment of larynx cancer, we witnessed a decrease in use of primary TL and an increase in the use of CRT and RT. In the period 1991-2000, 38% of patients with T3T4 hypopharynx cancer were treated with TL, which decreased to 20% in the period 2001-2010 (p<0.001). Interestingly, also in the Netherlands, the number of patients treated with CRT started to increase years before the feasibility of CRT was demonstrated by the publication of Lefebvre et al.

The balance between CRT and TL in T4 hypopharynx cancer

An important finding of this national study is the superior OS rate for patients with T4 hypopharynx cancer treated with TL versus CRT (29% vs. 24% at 5 years, p=0.039), similar to results obtained for T4 larynx cancer. Patients treated with single modality radiotherapy had a significantly worse OS at 5-years of 13%. Large population-based studies from the US have pointed towards a possible survival benefit in the surgical group as well. However, the results of these studies have to be interpreted with caution, as treatment results from population-based studies bear a risk of bias by indication. Furthermore, most large (national) databases do not include detailed information regarding type of treatment and/or report on other specific patient or tumor related variables. For example, in our national study, intent of treatment (curative versus palliative) was not recorded. While chemoradiotherapy is rarely applied as palliative treatment, single modality radiotherapy on the other hand can be given as a palliative treatment. This might in part explain the low OS of patients treated with single modality radiotherapy in our cohort.
Despite a lack of RCTs, evidence supporting the superior OS rate following TL in T4 hypopharynx cancer now seems to be accumulating. In 2014, Kuo et al. reported on 3,958 patients from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI), and demonstrated superior OS at 5-years in the surgical arm of 34.5% vs. 22.6% in the radiotherapy arm.12 A year later, Newman et al. reported on 6,637 hypopharynx cancer patients, also from the SEER database, and reported OS rates of 49% versus 37.8% for surgery versus radiotherapy at 5 years.13 Both SEER based studies however lacked information on the use of chemotherapy, which is likely applied in a part of the radiotherapy group. If these CRT patients would have been analyzed separately, a higher OS rate would probably have been reported for this subgroup.14 In the meta-analysis on the addition of chemotherapy by Blanchard et al., the 5-year absolute benefit for patients with hypopharynx cancer was estimated to be 3.9%, which does not fully explain the survival difference observed between TL and CRT in these two studies.15 Kuo et al. were able to assess the use of chemotherapy in a subsequent study, and in this analysis, survival rates were similar between CRT and TL (33.6% vs. 34.4%). However, the subgroup of patients treated with chemoradiotherapy for whom information was available, represented just 4.9% of the total study population.16

PREDICTING SURVIVAL

In current practice, when patients are counseled and ask for estimations on prognosis, most often the expected overall survival is presented based on their TNM classification and weighed against the proposed treatment. The TNM classification gives good estimations on a population level, but translates less well to the individual level. We aimed to optimize individual estimations on survival by developing risk prediction models for advanced larynx and hypopharynx cancer. Improved individualized risk estimations can aid the decisional process and possibly tailor treatment strategies, where for example high-risk patients might benefit from more intense (adjuvant) treatment strategies or follow-up regimens.

In chapters 3 and 4, we describe the development of two risk prediction models for advanced larynx and hypopharynx cancer. For both types cancer we succeeded in categorizing patients in low-, medium- or high-risk groups. The prediction model for advanced larynx cancer was based on a Cox proportional hazards model, constructed using a national database covering all patients with advanced T3T4 larynx cancer on which Timmermans et al. have published before.8 We validated the model using data from 5 external centers: Lund Medical Center, Sweden, University Hospital Leuven, Belgium, The Irish National Cancer Registry, and the Johns Hopkins and Emory University Hospitals from the US. Discriminative power was assessed using the C statistic; a C statistic of 0.50 equals chance and a C statistic of 1.0 indicates a perfect model. Discriminative capacity of our model was average with a C statistic of 0.65 after internal and 0.59 after external validation. Because the model left room for improvement with regard to individual risk predictions for advanced larynx cancer, we performed an additional exploratory analysis, which demonstrated that the addition of comorbidity data increased the discriminative ability of the model to 0.68. Although comorbidity information was limited to the patients treated in our own institute, the results in this subgroup suggests that adding comorbidity information might further improve the discriminative capacity of the model.

Based on the knowledge gained during the construction of the larynx model, we subsequently build a model to predict survival in hypopharynx cancer. In order to include more patient specific variables such as comorbidity, we used retrospectively collected data from the Netherlands Cancer Institute and 2 other dedicated head and neck centers in the Netherlands: University Medical Center Utrecht and Amsterdam Medical Center, Location VUMc. The model was build using the least absolute shrinkage and selection operator (LASSO) technique and consisted of the variables gender, subsite, TNM classification, Adult Comorbidity Evaluation score 27 (ACE27), body mass index (BMI), hemoglobin, albumin and leucocyte count. The model performed better than a model based on TNM classification alone, and yielded a slightly higher discriminative power of 0.62 after validation. Building further on recent data from Bril et al., the hypopharynx cancer model will likely be improved using data on sarcopenia, another relevant factor for OS that has been studied by several authors in recent years.17 Other improvements can be expected from the addition of certain biomarkers, for example the neutrophil-to-lymphocyte ratio (NLR)18, or features such as tumor volume19 or radiomics20. Adding such information to clinical prediction models may help to further improve robust individualized estimations of survival21, 22, 23. Ideally, these models should not only predict survival but also predict treatment response and toxicity, and are continuously re-evaluated and updated to maintain its clinical applicability.

FUNCTIONAL OUTCOMES

Besides providing individualized risk estimations, another aspect of great importance to patients is counseling about the expected quality of life following treatment. In our national cohort, we analyzed the cumulative incidence of salvage or functional TL following (chemo) radiotherapy with death as a competing endpoint. The cumulative incidence at 5-year was 7% for RT and 4% for CRT, with a cumulative incidence of death of respectively 68% and 64%. The low rate of salvage/functional TLs might reflect the fact that most recurrences in the hypopharynx region are considered to be inoperable. Although the term ‘laryngectomy free survival’ is often used to measure success of organ preservation, a more informative endpoint is however the term ‘laryngo-esophageal dysfunction free survival rate’ (LDFS).24 This definition is a composite endpoint combining time to local recurrence, death or
salvage TL and the presence of a feeding tube or tracheotomy at 2- or 5-years\textsuperscript{26}, and gives a better reflection of the functional success of organ preservation.

Driven by the limitations of our national study in which information on LDFS was missing, we performed an analysis of all patients treated for hypopharynx cancer in our institute between 1990-2013, described in chapter 5. In this retrospective study, we report an LDFS rate of 31% at 5-years. The first RCT by Lefebvre et al. reported a similar LDFS of 35% at 5 years, but in this endpoint, only death from local disease was used. When they used ‘death from other causes than local disease progression’ in this composite endpoint, it appeared to be 17% at 5 years\textsuperscript{3}.

A subsequent RCT reported even higher LDFS rates in patients treated with induction cisplatin (P), 5-fluorouracil (F) with docetaxel (T) followed by RT versus patients treated with induction PF followed by RT, respectively 67% versus 47% at 5-years\textsuperscript{5}. These authors however used a different definition of LDFS: ‘the presence of natural speech, absence of a tracheostomy, absence of a feeding tube for \geq 2 years after treatment or recurring pneumonia that required hospitalization’. Despite the superior results obtained following the induction TPF regimen, the increased toxicity resulting from the addition of docetaxel has limited the widespread acceptance of this regimen\textsuperscript{27}. Despite the fact that both RCTs used induction chemotherapy, the standard of care in The Netherlands is concurrent chemotherapy. In a meta-analysis comparing induction CT to concurrent CRT, the authors were unable to demonstrate a significant OS benefit in the patients treated with induction CT\textsuperscript{9}.

In our institutional study, we also reported on OS rate using a propensity score matched pair analysis of patients with T2-T4 hypopharynx cancer treated with TL versus CRT. As mentioned before, several tumor and patient related factors used implicitly or explicitly by physicians to indicate patients for a certain treatment, can confound the estimate of effect of treatment choice. Since the treatment paradigm has shifted towards favoring CRT instead of TL, year of diagnosis might also influence treatment choice and thus confound effect estimates. Using the propensity score matching approach, we aimed to control for these biases. In our cohort, we reported 5-year OS rate of 56% following TL versus 46% following CRT. This result was not statistically significant, possibly due to the low number of patients that remained after matching, and consequently the low power to detect statistical significance. Yet, the result is in line with that of previous observational studies. In a similar study, Tassler et al performed a propensity score adjusted analysis in a retrospectively collected cohort of 137 hypopharynx cancer patients treated at the University of Pittsburgh\textsuperscript{29}. Their propensity score model was based on T-classification (T4 patients were more likely to receive surgery) and year of diagnosis (patients in earlier years were more likely to be laryngectomized), and in the adjusted analyses these authors found a significant survival benefit in the surgical group over the CRT group\textsuperscript{29}.

In light of the increasing evidence favoring TL in terms of survival in patients with T4 hypopharynx cancer, the treatment choice between CRT and TL becomes even more difficult. How many survival years are patients willing to sacrifice in order to maintain their larynx? With this in mind, more attention should be paid to expected quality of life following treatment; especially since each patient might value the outcome differently\textsuperscript{26}, \textsuperscript{31}. The treatment decision between TL and CRT is a very personal one, and before making a choice, patients should be aware of the functional outcomes following TL and CRT, and should be counseled that each option can have a profound effect on quality of life. Kraaijenga et al. evaluated the long term toxicities following CRT and reported that 10-years after CRT, 54% had moderate to severe swallowing complaints and 14% was tube feeding dependent\textsuperscript{25}. On the other hand, TL has a significant impact on a patients’ quality of life and patients will have to cope with speech- and swallowing rehabilitation, issues we discussed in chapters 6, 7 and 8.

**REHABILITATION FOLLOWING TL**

Although the use of TL as primary treatment is decreasing over the past decades, it still remains a cornerstone in the treatment for head and neck cancer, although nowadays more often as salvage TL or TL for functional reasons. The three principal techniques to restore oral communication after TL are tracheoesophageal speech, esophageal speech and/or the use of an electrolarynx. Tracheoesophageal speech is the most frequently used method of speech rehabilitation in most Western countries. Although tracheoesophageal speech is associated with higher costs due to the need for recurrent replacements of voice prostheses (VPs), this method is reported to be associated with the best acoustic and perceptual outcomes\textsuperscript{33}.

In chapter 6 we studied the prosthetic vocal rehabilitation of a cohort of 232 consecutive TL patients over a period of 13 years. This is one of the larger reports available in literature. Similar to other studies\textsuperscript{24}, \textsuperscript{35}, we reported a declining device lifetime of now approximately 2 months in contrast to the 3 months reported in older studies.\textsuperscript{25}, \textsuperscript{27} Several explanations for the declining device lifetime have been suggested, such as the increased use of (chemo) radiotherapy in the adjuvant or neo-adjuvant setting, changes in diet and/or in biofilm composition on the VP\textsuperscript{30}, or the more comfortable antegrade replacement as compared to the old retrograde replacement method of the Provox\textsuperscript{29}. In countries such as Australia or the US, distance to the hospital is often perceived as another barrier for replacement.
Although the driving distance to a hospital in the Netherlands is almost never beyond 30-45 minutes, surprisingly, even with a median driving distance of 26 minutes in our cohort, we observed a significant effect of driving distance on device lifetime; the longer the driving distance, the longer the device lifetime. This effect was more pronounced in the non-standard replacements for TEP-tract related problems such as hypertrophy or infection of the TEP-tract. This suggests that patients recognize these issues less well as a reason to visit the hospital as compared to the standard leakage through.

Another aspect that might play a role in the relatively low device lifetime is the fact that all patients receive reimbursement for voice prostheses. Since patients in The Netherlands or for example Germany are not challenged by financial constraints, average device lifetimes of up to 17 months as reported in a Turkish cohort are a rare phenomenon in the Netherlands. However, in light of the increasing health care costs, physicians have a social responsibility in this aspect to manage these costs, determine whether there is a solid reason for replacement, and to adequately determine which patients might benefit from more expensive devices such as the Provox ActiValve.

In 2003, Hilgers et al. first reported on the Provox ActiValve. This prosthetic device is equipped with Candida-resistant fluoroplastic material and has a small magnet that prevents inadvertent valve opening. This device appeared to have a highly significant average 14-fold increase in device lifetime. The authors therefore suggested that using this (more expensive) VP would be cost-effective in patients known with relative low device lifetime.

In our recent study cohort, we were similarly able to demonstrate a significant increased device lifetime when using the ActiValve. During follow-up, 30% of patients (n = 69) received an ActiValve, generally given to patients that show a device lifetime < 2 months. Within these 69 patients, the device lifetime of a regular VP was 54 days, whereas the device lifetime of an ActiValve in this group was respectively 143 and 186 days for the ActiValve Light and Strong. A cost-effective analysis on the use of different VPs in our institute will be undertaken in a future study.

While the ActiValve was designed in order to improve device lifetime of patients experiencing mostly transprosthetic leakage problems and/or underpressure issues, the Provox Vega XtraSeal was designed to address recurrent periprosthetic leakage. This prosthesis has an additional thin and extended esophageal flange to provide a better mucosal seal. Periprosthetic leakage is a less frequently observed problem than transprosthetic leakage, but it appears to be difficult to solve. In our device lifetime study we described several solutions for this problem. In general, first the underlying problems causing periprosthetic leakage should be addressed in order to achieve long-term success, for example by prescribing proton pump inhibitors for gastroesophageal reflux, often encountered in TL patients. For the short-term solution, temporary removal of the VP to allow for natural shrinkage and/or downsizing of the VP can be tried, with or without placing a washer on the tracheal or esophageal side. If the problem persists, either a purse string suture or injection of bio-material can be tried, and finally surgical closure followed by a secondary TEP puncture. In chapter 7 we analyze the success of this new prosthetic device. The median device lifetime increased from 38 to 68 days when using the XtraSeal, and only in 1/26 cases the XtraSeal had to be removed because of periprosthetic leakage. Despite the small sample size, it seems reasonable to conclude that this novel device is a valuable new tool to solve periprosthetic leakage, further improving the long-term durability of tracheoesophageal speech.

**SWALLOWING REHABILITATION**

Rehabilitation following TL focuses mainly on vocal, pulmonary, and olactory rehabilitation, but swallowing rehabilitation for dysphagia following TL is another aspect that requires special attention. A recent review reported a prevalence of dysphagia after TL to range from 35-89%. Since most TL patients have been treated with radiotherapy, and in certain cases with chemotherapy as well, dysphagia following TL can be multifactorial. Dysphagia in laryngectomized patients can result from anatomical changes following surgery creating strictures or a narrowed lumen, functional problems due to (chemo)radiotherapy induced xerostomia, fibrosis or stricture formation following CQRT or reduced coordination of swallowing muscles.

After TL, especially when also (chemo)radiotherapy has been part of the treatment protocol, pharyngoesophageal stenosis is the main culprit of dysphagia, and often dilatation is required to resolve this issue. In chapter 8 we focused on swallowing complaints following TL that necessitated one or more dilatation procedures. Although dilatation procedures are well described in literature, there are very few studies describing the incidence, success rate and complications of dilatation in TL patients. In our cohort of 477 consecutive patients laryngectomized for any indications (primary, salvage, dysfunctional) in two major Head and Neck Cancer Centers in the Netherlands, we found a cumulative incidence of 22.8% at 5-years for dysphagia necessitating dilatation. In total, we analyzed 968 dilatation procedures. The median number of procedures per patient was 3 (range...
1-113). Risk factors for a dilatation procedure were female gender, a hypopharynx tumor and chemoradiotherapy before or after TL. Chemoradiotherapy before or after the TL appeared to have the strongest effect on dysphagia following TL, which is not surprising as several studies have demonstrated a high incidence of dysphagia following CRT. Lee et al. specifically evaluated risk factors for stricture formation following CRT and reported female gender and a hypopharynx tumor to be significant predictive factors for stricture formation, besides twice-daily radiation fractionation. The crude incidence of stricture formation in their cohort was 21%.

The main risk factor for a major complication appeared to be a dilatation procedure under general anesthesia. In our cohort, most patients who complain of dysphagia following TL are first subjected to an endoscopic examination under general anesthesia in order to rule out a possible recurrence. When this examination is combined with the first dilatation, the physician will not get feedback from the patient, indicating pain/irritation from a (too) large dilator. Possibly this imposes a higher risk on a transmural perforation. Although we cannot exactly point out the underlying cause for the increased risk of major complications following dilatation under general anesthesia, physicians should be extra careful in dilating new patients, who suffer from stenosis following TL.

Our cohort was more or less evenly split between patients that required 1-3 dilatations versus patients that required serial dilatations. The need for serial dilatation implies repeated hospital visits and associated health care costs. One of the patients in our TL cohort had learned how to self-dilate. This could be a valuable alternative to the repeated hospital visits, if proven to be safe. Because we could not retrospectively assess the number of dilatations and the success rate of this patient, he was excluded from analysis. Some small retrospective case studies (ranging from 16-32 patients) evaluating the safety and efficacy of this procedure, however, suggest that self-dilatation can be the treatment of choice for selected patients with refractory esophageal strictures.

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Counseling cancer patients on treatment options is difficult and becomes even more challenging in a setting where there is no ‘best treatment’ option, or when all options interfere significantly with quality of life. In order to improve patient counseling and shared decision making concerning the treatment options TL, CRT or RT, the availability of a patient decision aid (PDA) for patients with advanced larynx cancer would be of great value. There is ample evidence that shared decision-making and improved health communication improves patient outcomes and leads to more patient satisfaction.

In chapter 9 we describe the development of such a PDA for advanced larynx cancer patients, who we hope to empower by giving them more knowledge on the different treatment options. Based on the guidelines as set out by the International Patient Decision Aid Standards (IPDAS), we conducted several semi-structured and in-depth interviews with patients and physicians during three developmental phases. Patients and doctors agreed to the need for such a PDA. Several studies have indeed indicated that counseling of TL patients is in need for improvement. In a UK national survey, 84% of surgeons reported to discuss the diagnosis of cancer and the treatment option TL in the same consultation, which, on average, lasted 15 minutes. A review on the current counseling in the UK reported that the majority of patients considered counseling to be inadequate; up to 20% of patients were not aware of the consequence of loss of normal voice. Similarly, van de Sluis et al. who interviewed several female laryngectomees, reported that patients were often unaware of, or unprepared for, the challenges they would experience following their TL. Some of them reported they barely captured any of the information provided during the counseling process.
The results of our study described in chapter 9, indicate that an online PDA for advanced larynx cancer can be a valuable addition to the current counseling process. Head and neck cancer patients on average have a relatively low level of education, and most physicians in our study indicated that they perceived this as a barrier to good patient counseling. The interviewed patients, also those with a high level of education, indicated that they often could not remember the information given during the counseling process, and that repetition of information would be very useful. To test the feasibility of and satisfaction with our newly developed PDA in clinical practice, we started a prospective multicenter trial in The Netherlands.

**FUTURE PERSPECTIVES**

While the studies described in this thesis have improved our knowledge on survival in hypopharynx cancer following different treatments, robust overall survival figures are preferably derived from randomized trials. However, in current practice, setting up an RCT comparing TL with CRT seems near to impossible. An important issue in this respect, is the recent emergence of immunotherapy in (head and neck) cancer treatment. While most advancements in immunotherapy have been made in targeting melanoma, several institutes around the world are now exploring the possibilities of treating head and neck cancer patients with immunotherapy. Currently, in our institute, the neo-adjuvant administration of nivolumab and ipilimumab before surgery is being tested in a phase II single arm design (Clinical trials number NCT03003637). It seems that immunotherapy has great potential to alter the current treatment dogmas, but for head and neck cancer, until now, these antibodies are administered only in experimental settings. It remains speculative how TL and/or CRT will be replaced by this new discovery, and whether TL eventually can be abandoned or if it will always remain necessary, either as salvage treatment or possibly even as a primary treatment. It certainly will take several years before the results of the first large phase III trials are published and we might witness a shifting treatment paradigm again. In light of the current poor overall survival rate for hypopharynx cancer, any improvement to the current treatments options would be most welcome.

The above-mentioned studies offer great potential to alter the standard of care in advanced larynx and hypopharynx cancer on the long-term. Meanwhile, on the short term a focus on prospective, standardized data collection will greatly attribute to our current understanding of this disease. The Dutch Head and Neck Working group has recently set up a cooperation with the DICA (Dutch Institute for Clinical Auditing), which will facilitate a national monitoring of a pre-specified set of quality criteria. Based on this planned data collection, covering several medical aspects and patient reported outcome measurements (PROMS), the working group will internally evaluate the quality of care. Being able to compare not only oncological, but also functional outcomes and PROMS, is of great value. Especially in the study of rare tumors, where most studies report on small, heterogeneous patient groups, and the risk of selection or treatment bias is high, such national databases will greatly improve our knowledge.

Whatever the outcome of the above described studies will be, adequate patient counseling should always be a cornerstone of treatment. Building on the experiences of the PDA for advanced larynx cancer, we are now developing PDAs targeting other types of head and neck cancer. An important consideration in these PDAs is that, after successful introduction in clinical care, they should be checked and updated regularly to maintain its validity. Likewise, the above described clinical prediction models for advanced larynx and hypopharynx cancer should be updated using new data whenever this becomes available. Hopefully we will witness several important changes in the coming decade, and further improve survival and quality of life of patients with advanced larynx and hypopharynx cancer.


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