Recent Landmark Studies on Head and Neck Cancers: Evidence-Based Fundamentals of Modern Therapeutic Approaches



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Abstract

Evidence-based medicine, established on prospective studies and related algorithms is living its golden age in recent years. Within the last few decades, medical knowledge has been systematically produced, categorized, and spread in a way never seen before. One of the most important factors in realizing this situation is the expansion of the communication facilities. The area of the management of head and neck cancers was also affected by these advances, and studies with high-level evidence became the mainstay in the determination of the

Introduction

The philosophical foundations of the concept of evidence-based medicine (EBM) date back to the mid-19th century. In fact, this naming is not old and has been put forward by Sackett et al. (1). EBM can be roughly defined as "rational and reasonable use of the best level of evidence in the care and treatment of individuals" (1). However, in EBM practice, not only evidence but also experience and knowledge of the physician and preferences of the patient are taken into consideration.

As this concept becomes widespread, the question as to what is the best level of evidence has emerged, and in response to this question, the need to form a hierarchy of evidence arose (2). In this hierarchy level, although the first level or studies reaching to the highest level of evidence are prospective randomized controlled studies, case series and expert opinions are placed in the 4th and 5th levels, which are the lowest level of evidence. This new state gave rise to lesser consideration for experiences and retrospective studies based on experiences of physicians, by other physicians and medicine society compared to the past. As a result, an opinion of reaching better standards of medical care, trying new treatment methods, and developing traditional medicine practices has emerged, and studies have begun to advance in this direction.

management strategies. However, probably almost all of these studies are about non-surgical modalities, and studies with high-level evidence regarding the surgical treatment of head and neck cancers are scarce. In this paper, important studies on head and neck cancers and their results will be reviewed.

Keywords: Head and neck cancers, prospective studies, evidence-based medicine

Nowadays, although EBM increasingly occupies more space at the base of medical practices, there are also criticisms regarding EBM. The most important criticisms are that there has not been any study in several subjects, some practitioners are trying to strictly implement EBM, delays in spreading the current knowledge, difficulties to access information and to rapidly renew knowledge. Aside from planning and realization of studies having a high level of evidence, another important problem is partiality when industrial support is provided. According to a meta-analysis conducted by Bhandari et al. (3), the results tend to be in favor of the industry in the studies supported by that particular industry.

It is almost impossible to find substantial funds from the public or private sector for conducting studies that will attain results other than valid medical approaches and habits. Another important point is the difficulty to publish studies with negative results. Although the papers regarding an effective treatment method are accepted more easily, those indicating ineffective treatment methods are somehow considered invaluable (4).

Other important points that should be considered while the results of studies with a high-evidence level for the treatment methods are to be applied



Address for Correspondence: Utku Aydil, Gazi Üniversitesi Tıp Fakültesi, Kulak Burun Boğaz ve Hastalıkları Anabilim Dalı, Ankara, Turkey Phone: +90 312 202 64 47 E-mail: utkuaydil@yahoo.com Received Date: 26.11.2014 Accepted Date: 14.01.2015

© Copyright 2015 by Official Journal of the Turkish Society of Otorhinolaryngology and Head and Neck Surgery Available online at www.turkarchotorhinolaryngol.org © Telif Hakkı 2015 Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği Makale metnine www.turkarchotorhinolaryngol.org web sayfasından ulaşılabilir. Dol:10.5152/tao.2015.791 to field of medical practice are that these studies are conducted at the centers having high-quality standards and the criteria to be included to the study are generally strict. As a result of these, high-risk patients and some patients expected to have a worse treatment response can be excluded from the study, and the physicians working in the field who apply the treatment methods supported with studies having high level of evidence may not obtain the same results.

The principles that are valid for the treatment of all cancer types are also used in the treatment of head and neck cancers. The first of these is the selection of the treatment method providing the highest probability of survival. The second principle is the selection of the treatment method providing higher level of quality of life and better functional and cosmetic results in the presence of more than one treatment preference providing similar survival results. However, survival cannot be foregone for the protection of one organ or for a better functional or cosmetic result. This state is also seen in studies planned or conducted in association with head and neck cancers (5, 6). In the surgical or non-surgical studies regarding different applications to provide an advantage for a better quality of life and protection of an organ, it is indicated that the survival rates are not below the current standard applications. If there is worsening with regard to survival, this new modality cannot be evaluated among standard treatment alternatives. In the recent years, studies regarding head and neck cancers have been concentrated on the quality of life; however, efforts to enhance the survival have remained in the background (5, 6). Consequently, as there has not been any enhancement in the survival rates, particularly in some head and neck cancers, some minor deterioration has been observed (5-7).

When evaluated with regard to head and neck cancers, it is observed that almost all of the important studies having high levels of evidence are non-surgical. These studies having high level of evidence have begun to be conducted in the last three decades. Almost all of the studies regarding the surgical treatment of head and neck cancers are retrospective or have a low level of evidence. Therefore, in this review, studies published in the last 25 years regarding non-surgical treatments in head and neck cancers have been included.

The Emergence of the Concept of Protection of the Larynx with Non-surgical Methods in Locally Advanced Laryngeal Cancer: Veteran (VA) Study

Until two decades ago, surgical treatment, namely total laryngectomy (TL) was preferred to radiotherapy because of its survival advantage in locally advanced laryngeal cancer. For the first time, it was indicated with VA study that it may be possible to locally treat advanced disease in a non-surgical manner by avoiding TL as well as without negatively affecting survival (8). Although some pilot studies reported promising results with regard to induction chemotherapy (IC) in the beginning of the 90s, the preliminary results of multicenter Veteran study were vigorously presenting a new treatment strategy (9, 10).

In this study involving resectable 332 stage III/IV, patients were equally divided into two groups, and two cycles of platinum-fluorouracil (PF) therapy were administered to the first group; 18–21 days after the second cure was completed, the clinical tumor response was observed. Third cure PF was administered to the cases having a decrease in the tumor size at least by half; then, 6600–7600 cGy was applied to the primary region and necessary doses of RT were administered to the neck depending on the disease. TL and adjuvant RT were applied to the cases demonstrating insufficient response or those that indicated progression.

In this study, complete and partial response rates reported in the primary organ (larynx) were 31% and 54% after two cures, respectively. The full response rate after three cures increased to 49%. The mortality rate during IC was reported as 3%, and 12 (7%) patients could not complete the therapy because of toxicity. In the study having an average follow-up of 33 months, 2-year survival rates were reported as 68% in both groups. Although there was not a statistically significant difference, disease-free survival tended to be low as expected in the group receiving IC/ RT. Systemic relapses and second primary tumors in the surgical group were observed more often, whereas local relapses were more often observed in the IC/RT group. Larynx preservation rate in the group receiving IC was reported as 64% at the beginning. Half of the laryngectomy procedures in this group were performed after IC, and the other half was performed after RT. When looked at practically, at the end of a median follow-up of 33 months, it was reported that 101 (61%) of 166 patients were alive and 65 patients (39%) had a functional larynx in the IC/RT group. These results both turned a new page in locally advanced laryngeal cancer treatment and was an inspiration to the studies conducted with chemotherapy in the field of locally advanced head and neck cancer treatment.

The Rise of Concomitant Chemoradiation: RTOG 91-11 Study

After it had been shown with veteran study that larynx preservation was possible in locally advanced disease with IC/RT without any change in the survival, IC and RT applications in the cases in which patients showed response have become popular. RTOG 91-11 was a study with three groups, but it did not have a surgical group. A total of 518 cases were involved in the study, which began immediately after VA study that was conducted between 1992 and 2000, and these were distributed randomly to RT (singly), IC/RT, and concomitant chemoradiotherapy (CRT) groups. T1 and high-volume T4 tumor cases were not involved in the study. The induction group of the study continued similar to the VA study. Cisplatin concentration of 100 mg/m² was administered to the patients in concomitant CRT group on the 1st, 22nd, and 43rd day while receiving RT.

The radiotherapy dose was 7000 cGy for primary tumor, and it was 7000 for N+ and 5000 cGy for N0 in the case of neck cancer. As opposed to the VA study, neck dissection was routinely conducted eight weeks after RT was completed in the presence of nodal metastasis larger than 3 cm or more than one nodal metastasis. In this study, it is remarkable that only the patients in one of the three groups received RT. Even for a scientific study, the use of an application in a study that was known to result in lower survival than the standard treatments gave rise to queries regarding ethics. Moreover, not having a surgical group in the study is a deficiency.

In this study, completion rate of IC in the induction group was 78%, and the rate of patients not being able to receive a third dose of cisplatin in concomitant CRT group was 23%. During a median follow-up of 3.8 years, preservation rate of larynx was reported to be 84%. This rate is higher than both IC (72%) and singly RT (67%) groups, and the difference between them is statistically significant. When considered with regard to general survival, no difference was reported with the 2- and 5-year rates among the three groups (2-year survival rates were 74%, 75%, and 76% and 5-year survival rates were 54%, 55%, and 56%). Disease-free survival was reported to be better than the other two groups. When considered with regard to locoregional control, concomitant CRT was found more successful than both IC and singly RT. Two-year disease-free survival in patients receiving concomitant therapy was upto 17% higher than the IC group and upto 22% higher than the RT group on an average. It was also detected in this study that adding chemotherapy to radiotherapy decreased distant metastasis frequency. Detection of the concomitant application that decreases laryngectomy at the rate of 43%, started the transition from IC to concomitant therapy. When it was found that IC did not have a remarkable superiority to RT application, successive applications of IC was stopped. The extensive results of RTOG 91-11 were also published in 2013 (12). According to the 5- and 10-year results, as detected before locoregional control and larynx preservation was better.

Indicating the Benefit of Adjuvant Concomitant Chemoradiotherapy in Cases with Resectable High-Risk Head and Neck Cancers: EORTC 22931 and RTOG 9501 Studies

Two multicenter studies coming from Europe and the US in 2004 succeeded in presenting the benefit of concomitant CRT application in adjuvant treatment in the cases with high-risk head and neck mucosal cancers (13, 14). In these two studies, it was attempted to determine whether or not adjuvant concomitant CRT application instead of singly RT can enhance locoregional control and survival in the cases in the high-risk group with regard to relapse. In the EORTC study, there were 334 cases; in the RTOG study, there were 459 cases. The cases having oral cavity, oropharynx, larynx, and hypopharynx cancers were involved in both studies. Inclusion criteria to the RTOG study were positive surgical margin, presence of two or more metastatic lymph nodes, or the presence of extracapsular spread.

In the EORTC study, locally advanced tumors (T3 and T4), advanced nodal tumors (N2 and above), extranodal spread, positive surgical margin, perineural invasion, tumors having adverse pathological features, such as vascular tumor embolism, and patients having oral and oropharyngeal cancers with 4th or 5th level metastasis were involved. In both studies, in one group, in addition to RT after surgical resection, 100 mg/m² of cisplatin on 1st, 22nd, and 43rd days was administered; in the other group, patients received only RT. In the RTOG study, as a result of a median follow-up of 46 months, locoregional control in the CRT group was higher at a rate of 10%, and there was a statistically significant increase in disease-free survival. However, on the other hand, a toxicity of grade 3 and above increased from 34% to 77%.

In the EORTC study, the median follow-up period was 60 months. On an addition of chemotherapy, the improvement was 11% in the survival rate and 13% in the general survival without 5-year tumor progression. While 5-year cumulative locoregional relapse incidence was 31% in the adjuvant RT group, it reduced to 18% when CT was added. Distant metastasis rates in both studies were not affected from CT addition. There was no data regarding the region-specific benefit of combined application because subgroup analyses were not conducted in both studies. Moreover, it was unclear whether combined treatment provided benefit for all high-risk factors, which were determined as inclusion criteria, or for some of these factors. However, these two studies strengthened the position of CT as part of the adjuvant treatment of head and neck cancer treatment.

Can the Effectiveness of Radiotherapy be Enhanced without Increasing the Toxicity of Radiotherapy using Goal-Directed Agents?: Bonner's Study

After having indicated the benefit of CT addition to RT in laryngeal cancer, a significant increase in the use of CT occurred in all mucosal head and neck cancers; however, this resulted in associated toxicity problems. Bonner's study was published in 2006 (15). In this phase III study, locoregionally advanced 424 cases were involved, and there were a total of two groups.

While the cases in the first group only received RT, cetuximab, a monoclonal antibody against epidermal growth factor receptor, was administered weekly to the cases in the second group in addition to RT. In this study, patients having oropharyngeal, laryngeal, and hypopharyngeal cancers were involved. In the study in which the median follow-up period was 54 months, the duration of locoregional control was 24.4 and 14.9 months for cetuximab and singly RT groups, respectively; the median duration of life was 49.0 and 29.3 months respectively. One-, 2-, and 3-year locoregional control rates were 63%, 50%, and 47% for the cetuximab group and 55%, 41%, 34% for the singly RT group, respectively. There was no difference among the groups with respect to distant metastasis frequency. Although there was no mortality associated with cetuximab, treatment could not be continued in 6% of the patients and drug dose had to be lowered in 5% of the patients as well as there were delays in treatment owing to eruption. With respect to toxicity, there was no difference between the two groups apart from acneiform eruption, and infusion-related cases and cetuximab did not increase the common toxic effects of RT.

This study attempted to convey the following message: CT leads to an increase in toxicity associated with RT; however, if one uses cetuximab, similar results to conventional concomitant CRT can be obtained, thereby avoiding additional toxicity. However, before interpreting the results as such, it is necessary to emphasize some deficiencies and important points. First, in this study, lack of platinum-based concomitant CRT group is an important deficiency. Second, although subgroup analysis was not conducted in the study, when the results were analyzed, it is understood that cetuximab did not provide an oncological benefit in laryngeal and hypopharyngeal cancers. Third, although more than half of the patients have oropharyngeal cancer, their HPV states are not known, and there is no data regarding the effect of cetuximab according to the HPV state. Finally, this study is highly related to the industry, and 13 of the 17 authors worked for the sponsor companies, received salary or material support, and had some sort of relationship based on self-interest. These points should be taken into consideration while evaluating this study.

Induction Chemotherapy Application is not Beneficial before Concomitant Treatment: DeCIDE and PARADIGM Studies

After the superiority of the concomitant treatment over sequential therapy has been confirmed, concomitant CRT application has become the standard non-surgical organ-preserving treatment in locally advanced laryngeal cancers (16, 17). Meanwhile, concomitant CRT have been started to be applied more commonly in the treatment of head and neck cancers apart from its application in laryngeal cancers (18). Concomitant CRT has now begun to be frequently administered in all nasopharyngeal cancers out of T1, locally advanced oropharyngeal cancers, and hypopharyngeal cancers. Meanwhile, administering IC before concomitant application has become popular, particularly in Europe. However, because there was no sufficient evidence related to administering IC before concomitant application, these protocols could not be included in the guidelines and were not applied in the US (17).

However, the results of a phase II study published in Italy supported induction treatment (19). In this study, complete radiological recovery was evaluated as the end point; full response rates were found to be 50% and 21% in the groups with and without induction, respectively. When the inclusion criteria of this industry-supported study are considered, it was remarkable that only unresectable patients and patients evaluated as having a very low chance of cure were involved in the study. Moreover, no laryngeal cancer case was involved in the study. Subsequently, two recent studies had to be completed earlier, thereby disappointing some supporters of the induction CT. While the PARADIGM study was completed early and its results were published, the DeCIDE study was published even before it was completed, and its initial results were reported (20, 21). The reason for the early completion of both studies was that the desired number of patients could not be obtained and survival advantage could not be detected. In the PARADIGM study, the inclusion criteria were similar to those in the Italian study, but the cases with laryngeal cancer were also included in the study. It is said that no definite result was obtained in the study completed with 145 patients. Moreover, it was found that induction did not provide an advantage with regard to both general survival and survival with progression, and that concomitant therapy without induction resulted in higher survival rates. Moreover, an apparent increase was detected in the frequency of febrile neutropenia in the induction group. Furthermore, the consequence of the DeCIDE study was similar. This study included only patients in the N2 and N3 nodal stages, and a total of 285 patients were recruited. Although severe toxicity was observed more frequently in the induction group, no difference was found in general survival, remote metastasis, or recurrence. In both studies, more than half of the patients had oropharyngeal cancer. In the PARADIGM study, HPV positivity was not examined, but in the DeCIDE study, it was examined in some patients with oropharyngeal cancer. Moreover, in the DeCIDE study, subgroup analyses were also performed, and it was found that oncological results were not different based on HPV positivity, localization, and nodal stage. Another original result of the DeCIDE study was that a non-platinum-based protocol (taxane, fluorouracil, and hydroxyurea) attained a locoregional control rate of approximately 90% in concomitant therapy. According to these studies, it was understood that an induction before concomitant treatment did not provide any benefit in unresectable head and neck cancers or advanced nodal stage. However, despite this evidence, an induction before the concomitant treatment in locally advanced laryngeal cancers is still being commonly carried out in Europe for "forecasting possible results of treatment" (22, 23).

Phase III Studies on Taxane/Platinum/Fluorouracil Combination (TPF)

The first two of these studies are the TAX323 and TAX324 studies (24, 25). In these two phase III studies published at the same time in 2007, the classical PF combination and taxane added form of this combination (TPF) was compared during induction. These studies were conducted with patients having locally advanced and unresectable head and neck cancers, and the addition of taxane was reported to provide a significant survival advantage in both studies.

In the TAX323 study, survival time without median progression

in TPF and PF groups was 11.0 and 8.2 months, respectively. In the TAX324 study, the median general survival time was reported to be 71 and 30 months in TPF and PF groups, respectively. However, the cost of these results was seriously increased toxicity. Indeed, similar findings were reported in a phase III study known as the "Spanish study," which was published 2 years before the two TAX studies (26). On the other hand, the survival advantage was demonstrated only in unresectable patients in this study. Another phase III study, in which the location of the larynx was evaluated, was published in 2009 (27). This study included 213 patients with locally advanced larynx and hypopharyngeal cancer. Three cures of TPF were used in one group, and three cures of PF were used in another group as neoadjuvant treatments. Three-year larynx preservation rate was found to be 70.3% in the TPF group and 57.5% in the PF group. According to this study, the addition of taxane to neoadjuvant PF implementation for the aim of larynx preservation affects both the response and preservation rate positively. However, while interpreting these promising results, some data related to the study should be reviewed. Without and delay and decreased dose, the rate of receiving complete induction treatment was 32% in the PF group, but 62% in the TPF group. This means that, TPF seems to be tolerated better. While all of the patients receiving RT after induction were those responding to induction in the TPF group, 6 patients who had refused surgery were also given RT in the PF group. Moreover, although the rate of patients receiving concomitant CRT after induction was a higher to some extent (20.0% vs. 15.8%), it was still very low. Despite the fact that the result of this study seems to be in favor of TPF, the results should be approached cautiously. Furthermore, the study mostly consists of patients receiving sequential therapy, and its contribution to practical applications can be discussed at a time when the superiority of concomitant treatment is demonstrated.

Finally, in a phase III study conducted in China, the effect of neoadjuvant therapy with TPF before surgical and adjuvant treatments were investigated in locally advanced cancer of the oral cavity; however, the survival advantage could not be revealed (28).

Other Studies

In addition to the studies mentioned above, there are many studies that are valuable, but cannot be individually evaluated here. One of them is the alternate CT/RT study conducted by Lefebvre et al. (29), that could not be "popular" because of the probability that expected results were not obtained (EORTC 24954). Following VA study, this study is one of the second-generation larynx preservation studies together with the RTOG91-11 study. In this study, four cures of PF chemotherapy and 20-Gy RT cures were administered in an alternate manner (three 20-Gy RT between CT cures), and they were compared with a classical sequential schema used in the VA study. Differently, four cures of PF were administered instead of three cures in the sequential schema. As a result, no difference was found with re-

gard to survival or larynx preservation.

The same consequence is also valid for another study conducted by Gibson et al. (30) in 2005. Based on the results of some previous phase II studies suggesting that inclusion of taxane instead of fluorouracil in PF combination could provide survival advantage; this phase III study was conducted with patients having locally advanced, recurrent, and metastatic disease. Unfortunately, no positive result was obtained in terms of survival, response, or toxicity.

It is known that concomitant CRT and accelerated RT applications in locally advanced head and neck cancers positively affect oncological results independent of each other. In a French phase III study published in 2012, the non-metastatic stages III and IV patients were divided into three groups. One group was given the conventional concomitant CRT, another group was given accelerated RT-CT, and the final group was given only accelerated RT (31). In the study evaluating survival without progression on more than 800 patients, the best results were obtained with the conventional concomitant CRT schema. This study revealed that the acceleration of RT did not provide additional benefit in concomitant administration. Moreover, RT acceleration without chemotherapy resulted in statistically lower survival without progression than the conventional concomitant CRT schema. This study once again demonstrated the effect of chemotherapy when administered with RT.

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