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Review Article

On Recurrence Detection of Squamous Cell Carcinoma of The Head and Neck; A Critical Survey

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Abstract

Current follow-up protocols of squamous cell carcinoma of the head and neck (SCCHN) rely on detection of recurrence at an asymptomatic stage. The evidence supporting a survival benefit of asymptomatic recurrence detection is relatively weak. These protocols are entirely based on assumptions and tradition, not evidence. There is ample evidence supporting the notion that most recurrences are diagnosed through patient symptoms. The staggering preponderance of symptomatic recurrence suggests that patients lack knowledge concerning symptoms that signify recurrence. Patient education should therefore be regarded a key factor of follow-up. We strongly emphasize the need for an easily accessible and adequate description of red flag symptoms that might signify recurrence. Having proper information, patients are less likely to forget, withhold or disregard these symptoms. Adequate incorporation of symptomatic recurrence might prove beneficial in terms of survival. Improvement of surveillance protocols for patients treated for SCCHN is of great concern considering the lives at stake, expense of treatment and follow-up. Local recurrence is the most important prognostic factor in SCCHN and incomplete surgical margins the single most decisive factor concerning recurrence. Local recurrence can arise close to the site of the initial primary tumor, either from cells left behind after surgery (minimal residual disease/cancer) and further deterioration of premalignant epithelial changes left behind after an excision. Several techniques have been developed for securing resection margins and identification of premalignant epithelial changes, thereby replacing the need for frozen sections. Genetic studies have unravelled the difference between local recurrence and secondary malignant tumors (SMTs) that necessitate significant changes in the timing and duration of follow-up appointments and renewed listing of SMTs.

Conclusion: Today's simple 'one size fits all' surveillance protocols for SCCHN are inadequate. Rethinking of today's follow-up procedure is absolutely required.

Keywords: Cancer; head and neck; squamous cell carcinoma; recurrence; surveillance; second malignant tumours; treatment; survival, prognosis

Introduction

Approximately 90% of all cancers of the head and neck are squamous cell carcinomas (SCCHN).The recurrence rate of these tumors is exceptional high. A period of surveillance after curative treatment of squamous cell carcinoma of the head and neck (SCCHN) is, therefore considered an essential part of the treatment. Apparently, there is a unanimous agreement that post-treatment follow-up with regular specialist-led clinical examination allows detection of recurrence, whether local, regional, at distant sites or secondary malignant tumors (SMT) at an asymptomatic stage, which in turn facilitates timely treatment with beneficial outcome and acceptable morbidity. The evidence supporting this assumption is, however, relatively weak. On the other hand, there is ample evidence supporting the notion that a substantial number of SCCHN recurrences are diagnosed through symptoms patients themselves present at regular or self-initiated outpatient appointments, but also for symptomatic recurrence the evidence of a survival benefit is poor [1,2]. Consequently, the ability to timely detection and treatment of recurrence remains an obstacle to long-term survival of SCCHN. Regular posttreatment consultations have other wide reaching and favorable outcomes beyond contributing to patient survival statistics:

a) Evaluation of the efficacy of the initial treatment

b) Detection and treatment of induced physical complications

c) Management of cancer- related psycho-social complaints [3]. To this list, it is justifiably adding a fourth item, identification and treatment of premalignant lesions.

Two prominent British otolaryngologists, Stell and Harrison, were probably the first to highlight the importance of follow-up of patients treated for head and neck cancer. In 1984 they rejected a statement questioning the need for follow-up of head and neck cancer patients by stating that "this was certainly not the perception of people treating head and neck cancer" [4]. the first study to report on the significance of follow-up of patients treated for SCCHN was presented in 1985 [5]. Twenty years later, Morton et al. [6] admitted that it was unclear whether surveillance really provided any survival advantage. The authors proposed a clinical trial in order to elucidate the significance of posttreatment surveillance. We were unable to ascertain whether such trial was carried out, possibly because of disillusionment over discouraging results from studies with a similar purpose, performed on patients with breast and colon cancer. The high rate of recurrence of SCCHN and unsatisfactory outcome of secondary treatment is poorly understood. Our objective is to point out and discuss some topics that may contribute to this unfortunate situation. It seems that tools, other than frozen sections, still is the preferred method for securing negative resection margins. Moreover, we want to draw attention to the consequence of current definitions of local recurrence and SMT and the possible significance of symptomatic recurrence.

The surveillance protocols for SCCHN have remained practically unchanged for many years, with only minor differences between national and international recommendations. It is to be regretted that existing follow-up SCCHN protocols are based entirely on suppositions and tradition, rather than on evidence. We gathered information from several sources, including personal experience at a multidisciplinary tertiary academic referral centre and available databases. A brief overview of epidemiology, pathogenesis is needed to better understand recurrence and prognosticators of SCCHN. We do not have a complete formula for an ultimate surveillance protocol. Nonetheless, we want to pesent some issues that future expert panels may consider when planning upcoming improved surveillance protocols for this group of patients.

Epidemiology

Head and neck cancer is one of the most common cancers worldwide. The epidemiology of SCCHN has shifted dramatically over the last 50 years. SCCHN was typically diagnosed in older (≥ 65 years) male persons in association with heavy use of tobacco and alcohol. Occupational exposure to carcinogens is a well-known cause of sino-nasal cancer [7]. High-income countries currently have the highest incidence of head and neck cancer overall, but mortality is highest in lower income countries [7]. HPV-associated oropharyngeal SCC represents a subset of head and neck cancer which is rapidly increasing in younger adults (< 45 years). HPV infection is primarily transmitted through orogenital intercourse. HPV transmission during childbirth is very low. The incidence of HPV-associated cancer is rising in all western countries. HPV, mainly type 16 and – to a lesser degree – type 18, is identified as a causal factor for this subtype of SCC. HPV associated oropharyngeal tumors arises in the deep crypts of tonsillar tissue. The viral oncoproteins E6 and E7 silence the two major tumor suppressor genes p53 and pRb [8]. Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer [9]. Patients with HPV-positive oropharyngeal cancers have a favorable prognosis compared to those who have HPV-negative tumors [10].

Pathobiology of SCCHN

The majority of, if not all, new SCCHNs develop from precancerous cells harboring cancer- associated genomic and molecular changes concealed in 'contaminated' mucosal cells. The initiation and progressive acquisition of genetic and epigenetic alterations often involve continuous mucosal changes from normal histology to hyperplasia, dysplasia, and carcinoma in situ and eventually invasive carcinoma. Genetic studies have substantiated Slaughter and co-workers the concept of field cancerization [11], e.g., areas of cells with premalignant changes, called patches. Within these fields, there are clusters of cells with cancer-associated genetic alterations with the potential of further deterioration [12,13]. Several authors have contributed to the description of the complex sequence of molecular alterations associated with various stages of head and neck cancer. These premalignant changes may manifest themselves as leukoplakia and erythroplakia [14-16], but precancerous lesions are more often both macro- and microscopically invisible [17]. Oral mucosa is the organ studied most intensively, but a multistage carcinogenesis has also been described in the oropharynx, larynx, lung, oesophagus and other organs [16]. Time, effort and expenditure could be saved if premalignant lesions could be traced and effectively treated. Novel therapies designed to decrease local recurrence rates in SCCHN should also focus on eradicating precursor lesions left behind after surgery [17]. In this connection it is encouraging to note the discovery of WEE1, seems to be promising chemopreventive target bothfor precancerous and cancer cells [18]. The oncogenic nature of high-risk HPVs is due to the immortalising and transforming properties of HPV oncoproteins E6 and E7, which target the p53 and pRB tumour suppressor pathways, respectively, rendering infected cells susceptible to mutations and cancer development. The preference of HPV for the oropharynx is still unexplained but may be related to the unique presence of transitional mucosa in the oropharynx, predominantly found in the tonsillar tissue and which shows histological similarities to the cervical mucosa [19].

Recurrence

It is impossible to give an exact figure for recurrence of SCCHN as the incidence varies according to tumor site, stage, timing and type of treatment as well as follow-up procedures. Nevertheless, rough estimates have suggested that the recurrence rate for early-stage tumors is approximately 20% and 30- 50% for locally advanced

tumors. In a huge material derived from Taiwan national health insurance showed that age clinical stage at diagnosis, comorbidity and time to relapse were independent significant factors of recurrence of SCCHN [20]. Hopefully, new primary treatment regimens will bring down the rate of recurrence of SCCHN.

Local recurrence

Local recurrence is the most common type of recurrence in SCCHN and the single most important prognostic factor that predisposes for local recurrence is incomplete surgical margins. 'Positive' margins explain recurrence either because of

a) Margin closeness to the tumor (within 0.5 cm),

b) Premalignant changes in the mucosal margin (field cancerization),

c) Cancer in-situ in the mucosal margin, and

d) Invasive microscopic cancer at the depth margin of the macroscopically resected tumor, denoted as minimal residual cancer/ disease (MRC/MRD) [13,21,22]. Doubts concerning resection margins and proven violated resection margins represent an indication for either re-excision or postoperative radiotherapy [23].

In 1995 Brennan et al. [24] demonstrated that a significant number of specimens collected from the resection margin after resections regarded microscopical radical still harbored cells with P53 mutations, thus proving the presence of tumor cells left behind after tumor resection where conventional histopathological assessment classified the margins as negative. Brennan's observations have been proved in later studies [25]. The presence of mutated p53 in the resection margin is a strong predictor of local recurrence and vice versa that absence of p53 as a marker for favorable prognosis [26]. The finding of p53-Abs in the sera of individuals who are at high risk of cancer, such as exposed workers or heavy smokers, indicates that they have promising potential in the early detection of cancer [27]. Radiation is used as the sole primary treatment and in combination with other therapies. Radiation kills cancer cells by damaging DNA beyond repair. When killed, the cells are broken down and removed. However, some cancer cells may escape eradication and regrow at some point in the future. A study on patients treated by radical radiotherapy and who subsequently underwent ablation for a recurrence showed that patients with positive resection margins had a poor outcome compared to those in whom the margins were negative [28]. There is considerable evidence supporting the idea that a significant number of preneoplastic lesions of the vocal cord progress to infiltrative cancer. For this reason, follow-up is considered an essential part of their treatment. The optimal length of follow-up has not been determined, but a proposal from the European Laryngological Society suggests that a classification into low- and high-risk dysplasia ought to define the intensity and length of surveillance [29].The term potentially premalignant oral epithelial lesions (PPOEL) has recently been used as a broad term to define both histologic and clinical lesions that have malignant potential [30]. Whether premalignant lesions are localised to the oral cavity or larynx nonsurgical treatment fall into the category of chemoprevention or observation. No doubt, prevention by quitting smoking is likely the best way to prevent cancer development in the upper aerodigestive tract.

There are controversies regarding reporting and interpretation of the status of resection margins [31]. Two forms of error can occur in frozen section margin evaluation: interpretive and sampling. The use of frozen sections margin-driven assessment is almost universally accepted as a reliable measure for margin assessment, but this approach has some well recognized pitfalls that surgeons must be aware of. Despite a pathologist's verdict of negative resection margins based on frozen sections a significant number of recurrences occur [32]. The surgeon may miss the area with residual tumor tissue and a margin may mistakenly be judged as "free". For several reasons, specimens taken from the resection margin must be generous because there is considerable shrinkage due to tissue elasticity and processing in the cryostat [33,34]. Freezing artefacts, bloated cell morphology and necrosis, size and variations in thickness of sections are factors that may jeopardize the reading of slides. There is also the possibility that malignant cells may be overlooked or invisible due to epithelial-mesenchymal transition (EMT) that plays an important role during invasion and metastases. During this process cancer cells switch their epithelial characteristics to mesenchymal elongated, motile cells with invasive characteristics. Having acquired a fiobroblast- like appearance they can no longer be microscopically identified as neoplastic cells [35]. Kain et al. [36] conducted a review on resection margins in oral oral SCC and concluded that a practice of specimen-driven margins assessment is preferable compared to margin analysis. Mutant Tp53 LigAmp analysis is a rapid, sensitive and quantitative method to investigate presence of occult tumor cells in the margins of SCCHN [37], but unfortunately unfit for intraoperative use.

Tools For Margin Assessment

Intraoperative frozen section cannot reliably eradicate positive final margins [38].Time, effort, expenses, patients suffering and death due to SCCHN could be reduced if accurate margin assessment could be performed intraoperatively. Several ingenious techniques have been developed for this purpose and some of the techniques in clinical use today are briefly described here. Narrow band imaging (NBI) refers to an optical imaging technique for endoscopic illumination with blue and green light is used for identification of capillaries within the mucosal surface in the upper aerodigestive tract is one of several sites in the body where NBI is in use. An abnormal capillary pattern is an accurate diagnostic marker of paraneoplastic and neoplastic lesions. NBI is easy to set up and operate and can also be used intraoperaoperatively [39]. Fluorescent imaging has been in use for several years been used in a wide variety of applications to assist detection, delineation, tissue sampling and excision of premalignant lesions and early-stage tumours of the oral cavity and larynx [40,41]. Whether

used with photodynamic drugs or without (autofluorecence) fluorescence imaging represents a serviceable complementary method, also to microlaryngoscopy for detecting and delineating laryngeal malignancies [42,43]. When comparing narrow band imaging and autofluorecence in imaging benign and malignant laryngopharyngeal lesions the former imaging mode had the best score for sensitivity and specificity [44].The confocal microscope is non-invasive specific fluorescent microscope that allows obtaining 3D images of the sample with good resolution resembling histological tissue evaluation without staining. This method also can be used in vivo [39]. Raman spectroscopy is a complex optical principle based on the interaction of photons with the target material producing a highly detailed biochemical 'fingerprint' of the sample. Raman spectroscopy is highly sensitive and specific and affords the ability to take recordings from very small sections of the target sample. Raman spectroscopy has shown its usefulness in a wide variety of clinical settings such as assessing resection margins in breast cancer and colon resections [45,46]. In the oral cavity Raman spectroscopy allows distinction of malignant and normal tissue [47] as well as in vivo identification of premalignant changes [48]. Looking into the future, Cui et al. [49] predict three promising directions. One is the rapid histology based on two-color surface enhanced Raman spectroscopy microscopy which can be used during cancer surgery. The second is in situ molecule-based diagnosis using handheld fast Raman imaging. The third is a multimodal imaging and spectroscopy system that integrate advantages of each modality and may offer better diagnosis for cancer [46]. Through intensive research the past couple of decades, Multiphoton Microscopy (MPM) has emerged as a powerful tool that produce 3 D images of biological structures comparable to traditional histopathology both in vivo and ex-vivo (virtual biopsies) [50,51].

Local recurrence vs. SMTs

It has often been difficult to ascertain beyond reasonable doubt whether a renewed tumor manifestation is a consequence of MRC or a secondary tumor that originates in the mucosa with premalignant changes close to the site of the original tumor. Genetic studies have unravelled any misunderstanding regarding recurrence and secondary malignancies, thereby presenting a revised version of local recurrence and SMTs. A molecular-based definition for a local recurrence is a tumor manifestation occurring at a distance less than 2 cm from the original tumor or within three years after the diagnosis of the initial (primary) tumor. If the distance between the recent tumor and the initial primary tumor is >2 cm or occurs > 3 years after the diagnosis of the initial tumor the new tumor manifestation is considered a SMT, also called a second field tumor (SFT) [14]. The definition of synchronous and metachronous SMT remains unchanged. It seems that these definitions are not yet generally accepted as there are very few authors who have used these definitions. We have admit being among several others who must accept that previous presentations of recurrence and SMT rates are unreliable. These new definitions imply that several clinical materials must be modernized. Moreover, these definitions suggest that what we have until now considered as late local recurrences are in fact SMTs. In addition to the surgical margins, the depth of tumor growth (thickness) of the primary tumor is a strong prognosticator not only for disease-specific survival (DSS) and overall survival (OS) [52], one of several studies that led to the inclusion of tumor depth in the latest UICC/AJC classification of malignant tumors.

Regional Recurrence

Presence of nodal disease is a strong determinant of treatment and prognosis. Treatment options for regional recurrence are still limited. In addition to proof of incomplete local resections, Brennan et al. [24] demonstrated that serial sections of lymph nodes stained for mutant p53 disclosed a significant number of lymph nodes negative with conventional one-section yet stained positive for p53. Despite the use of modern multimodality diagnostic imaging and ultrasound guided aspiration cytology (USgFNAC) the rate of false negative classification is approximately 20 %, possibly caused by inaccurate cytology. Real-time E48 Q-RT-PCR is an accurate technique for squamous cell detection in lymph node aspirates of HNSCC patients. The test should be routinely implemented in USgFNAC to diagnose cases for which cytological examination is not conclusive [53]. Clinically negative necks are often treated electively, either by irradiation or surgery. Both methods entail disadvantages. However, the latter has the advantage of being both diagnostic and therapeutic. In cases of negative radiological examination and USgFNAC it might be justified with a wait- and- see policy. A prerequisite for such a policy is a strict follow-up regimen [54]. Several studies have shown that the depth of the primary tumor represent a decisive factor for regional recurrence and outcome of early-stage oral SCC [55,56]. The critical depth has, however, not yet been established. Real-time E48 Q-RT-PCR is an accurate technique for squamous cell detection in lymph node aspirates of HNSCC patients. The assay shows an increase in sensitivity and frequency of reached diagnosis compared with cytology [53].

Distant Metastases

Spread to distant sites depends on the initial location of the primary tumor, initial T- and N stage, and absence of regional control [57]. Glottic tumors have the lowest and nasopharyngeal tumors the highest incidence of distant metastases [58]. Most distant metastases of SCCHN occur within two years of the initial diagnosis, with a median survival of only 7.5 months [57]. Pulmonary metastases account for more than 50

% Of all distant metastases, followed in sites by bone, liver and mediastinum [58,59]. One important indication why initial and later search for distant metastases is that presence of distant metastases has significant implication on treatment. The fact that we had and still have relatively little to offer these patients other than palliation may explain some degree of reluctance in disclosing distant metastases. Immunotherapy might become a successful second-line treatment option for selected patients.

Detection Of Recurrence

The preponderance of symptomatic recurrence in SCCHN is well recognized [2,3,5,60-63], but proof of a survival benefit for symptomatic recurrence is still weak. Conversely, there are some studies showing a survival benefit for asymptomatic recurrence [64-66]. In spite of a predominance of symptomatic recurrence there are studies that still show a survival benefit for asymptomatic recurrence [67,68]. Almost 30 years after the recognition of follow-up in SCCHN patients of follow-up of G. B. Snow [69] commented on the follow-up procedures by asking "How frequent, how thorough and for how long?" A generally accepted surveillance protocol for patients treated for this group of patients is still not satisfactory settled. It seems that there has been little recognition of the need for studies that might improve prediction of recurrence of advanced SCCHH. A generally accepted follow-up protocol is a matter of great concern, considering the number of lives at stake, the immense workload and expenditure of diagnostic procedures, treatment and surveillance of this group of cancer patients. There are no current data supporting modifications specific to the surveillance plan of patients with human papillomavirus-associated disease [70]. The prevailing national head and neck cancer societies seem to agree on a 'one size fits all' surveillance protocol. These schedules are too simple as they disregard the fact that the rate and site of recurrence depend on the primary site and clinical stage of the original tumor and several other variables. Some authors have therefore advertised for a more patient-focused individualized post-treatment follow-up policy based on already known unfavourable variables [71,72]. Nomograms is one of several mathematical methods that comply with this demand. Nomograms allow personalized treatment plans and outcome prediction of SCCHN [73-75]. An EU supported Big Data to Decide (BD2D) program for advanced SCCHN has been launched [76]. A Decision Support System (DSS) will be developed based on data from multiple subjects. Such studies combine demographics, diagnostic work-up (etiological, clinical, pathological, radiological and genomics), treatment data (surgery, radiotherapy, chemotherapy etc.), treatment response, quality of life data and complications [77]. The ultimate aim is to provide scientific derived personalized treatment decision-making and prognosis for any patient with this disease.

It is generally agreed that follow-up appointments should be particularly close for the first two years after treatment as the majority of recurrences occur in this time period. Our study showed that the majority of early recurrences were symptomatic and preferentially at the primary site. Early local recurrence was particularly conspicuous for early-stage tumors treated by surgery or radiotherapy alone or in combination. A study counting 1678 patients showed that regional and distant metsastases was a rare event beyond the third year after treatment. Local and regional recurrence was also relatively rare in the third-year posttreatment [2]. Thereafter, any reappearance of tumor manifestations at or close to the site of the originally tumor should be defined as SMTs [14].Follow-up beyond the third year therefore become search for distant metastases. For several reasons both clinicians and patients are responsible for non-adherence to prescribed follow-up protocols. Frequent follow-up consultations shortly after completed treatment has the advantage these patients are less likely to downplay important symptoms, thereby enhancing adherence to the follow-up protocol and preventing drop-outs and delay [78]. On the other hand, a negative clinical and/or radiological evaluation may provide a significant subjective reinforcement for a patient who sees a negative examination as a relief, giving a feeling of security. Such an assurance may, however, be false and could weaken a patient's attention to symptoms that might signify recurrence. Previous studies have shown that the frequency of follow-up does not influence recurrence detection rate or survival of SCCHN [70,79].The new definitions of local recurrence and SMT involve considerable revision of follow-up procedures. Any follow-up program should be flexible, allowing patients who are unable to follow a standardized surveillance scheme to attend appointments when suitable. We believe in the benefit of properly patient information/ education in red flag symptoms of recurrence. As prospective studies on surveillance of SCCHN have so far are scarce, we have high expectations concerning the results of the ongoing study by De Zoysa and coworkers at Guy's & St Thomas' Hospital in London [80]. In 2017 these authors presented a pilot study which was designed as a patient-centred post-treatment surveillance protocol delivered through a patient-held card to remind the patient of symptoms consistent with residual, recurrent disease and SMTs. Contact information was also included on the card. Compliance was initially exceptionally high. We fully agree with these authors who state that, by engaging patients in active participation in their own surveillance, non-attendance and loss to follow-up would be maintained at low levels. This study might provide important information concerning the significance of symptomatic recurrence in terms of survival and the optimal frequency of follow-up visits. Termination of hospital physician- or nurse-led follow-up does not mean that there is no longer a need for surveillance. Many patients suffer secondary complaints related to previous treatment and poor quality of life. Health professionals other than the head and neck surgeon or oncologist are likely to be better trained in handling such problems. Having received a case summary listing particular needs, medication and what they should check regularly, GPs are in charge of a patient's wellbeing. Clinical nurse specialists should always be available for unhurried consultations.

Patient's age

Most western countries define people older than 65 years as elderly and this group constitutes the fastest growing segment of the population in the west [81]. Elderly people are likely to bear the highest cancer burden in the coming years [82]. The treatment and follow-up surveillance of elderly patients will therefore be at the forefront in future daily clinical practice. Programs must be developed to ensure that the varied needs of elderly cancer survivors can be met. Elderly people represent a frail patient group as they are more likely to suffer from deterioration of functionality – declining physiological capacity, comorbidities, polypharmacy, poor nutritional status, reduced cognitive functioning and

problematic socio- economic issues. Nevertheless, chronologic age by itself is not an indication to abstain for treatment of SCCHN. [83,84]. Octogenarians undergoing major surgery suffer a higher rate of postoperative complications than younger patients and comorbidity is likely the most important predictor of outcome [85]. The fact that older patients are rarely included in clinical studies explain the scarce information regarding the possible benefit of salvage treatment in elderly patients, Interestingly, Clayman [86] in 1998 reported that the overall survival for octogenarians in the United States surgically treated for head and neck cancer equaled the survival of octogenarians of the general population. Having received compassionate information concerning possible complications, further deterioration of any kind of morbidity elderly patients might have from previous treatment it is not unreasonable that otherwise fit elderly patients with recurrence might benefit from salvage treatment and thereby spared the misery and devastating situation of death due to tumor progression.

Patient education

The staggering preponderance of symptomatic recurrence is a strong argument for considering it more closely. Several publications stress patient education as the key element of timely recurrence detection [1-3,63,70,87,88]. It is therefore surprising that the significance of symptomatic recurrence in terms of survival has not received more attention. For one site, glottic carcinoma, we observed a favorable outcome for symptomatic recurrence [89]. Agrawal et al. [90] demonstrated that self-diagnosis of recurrence of head and neck tumors and new primary disease was common, with symptoms or findings noted by patients before interaction with the clinician. The authors noted that the presence of such findings was perceived as trivial and did not motivate these patients to seek advice. In a later study Agrawal and colleagues [60] found no difference in survival between compliant and noncompliant patients and concluded that survival related more to variables associated with prior disease or recurrence location than to those associated with follow-up surveillance. We find it equally plausible that these patients were unfamiliar with symptoms that might signify recurrence and the severe consequences of not receiving immediate medical attention. Any patient delay of reporting red flag symptoms seriously affects secondary treatment, and the chance of successful survival has not been satisfactorily studied. It has been our and other researchers' [91] experience that the consequence of late diagnosis of recurrence is disastrous. Patients lacking knowledge of red flag symptoms and a failure in self-reporting represent an ignored negative prognostic factor. Regardless of how conscientious we are with our information when patients are discharged and at follow-up appointments, it is unlikely that all patients understand and retain all information provided. It is a demand that this information gap must be closed. As no formal list of alarming symptoms and signs that might signify recurrence exists, clinics or national societies responsible for treatment of head and neck cancer patients are urged to prepare brochures that, in simple language, describe red flag symptoms and signs of recurrence. These leaflets should also provide information on SMTs, treatment-related side effects and complications, as well as psychological problems and where to seek help. These leaflets ('End of treatment letters'), which should also be digitally available, should be handed out when patients are discharged. Having this information, patients may feel more secure and encouraged to actively participate in their own surveillance program and immediately respond if they experience anxieties [92]. It goes without saying that patients must also be fully advised of the very serious adverse effects of continued tobacco and alcohol abuse.

Second malignant tumors

SMT are the second most feared consequence of having once being diagnosed with SCCHN Annual percentages is the best way of presenting incidents of SMT's. Rate of SMT's within the upper aerodigestive tract (UADT) depend on the site and stage of the index tumor, gender, age and whether or not there is a continuous exposure to carcinogens (in particular alcohol and tobacco) and previous radiation therapy. Most studies, including a study from Norway report an annual rate of SMT is 3-4 % the first 10 years after treatment. The survival rate of local recurrence and SMT's and local recurrence was practically identical the three first years after treatment [93]. When comparing the rate of SMT for patients treated with initial radiotherapy and initial surgery the former treatment modality had the lowest SMT rate the first 5 years after treatment. There is a possibility that radiation treatment partly eradicates preneoplastic lesions [94], thereby temporary reducing development of SMT. The 20-year cumulative risk of SMTs in the aero-digestive tract in patients previously diagnosed with SCCHN has been estimated at 20 % [95]. It is questionable whether a possible yield in salvage justifies the workload and expense of long-lasting regular follow- up with the intention of diagnosing SMTs.

Nurse specialists

Hospital-based physician-led follow-up will often primarily focus on disease progression or recurrence and therefore frequently fails to meet secondary issues that play an important role to the welfare of head and neck cancer patients. Few cancers pose greater challenges than those in the head and neck. Our patients are often troubled by their appearance and physical complaints, as well as psychological, social and economic problems, all of which have a severe negative impact on their health-related quality of life (HRQoL) [88, 96-98]. Any hospital treating cancer patients should have departments dedicated to rehabilitation of cancer patients. The psychological and economic benefit of this service cannot be overestimated. The American Cancer Society has published an excellent extensive online continuing education activity program that gives recommendations for most problems patients treated for head and neck cancer may encounter [99]. For some years we have witnessed a gradual shift in physician-nurse tasks. In some oncological specialities, the role and responsibilities of nurse specialists have gradually been extended so that these nurses can take on duties previously performed by doctors, thereby reducing

strain on outpatient clinics and relieving doctors of aspects of the follow-up care [100,101].

These highly trained nurses have acquired the necessary skills and knowledge of medical and practical features of specific types of cancer to enable them to supervise follow-ups via regular telephone or video consultations. This follow-up procedure is consistent with the proposal by Stimpson [63] proposal of low-risk follow-up clinics for patients free of disease at two years who are likely to be cured. Close collaboration between the nurse specialists, the responsible physician and allied health personnel guarantees that alarming symptoms, complaints and other issues are adequately addressed. Nurse-led follow-up is practical as it is effective, safe, accurate and less costly than physician-led follow-up and widely accepted by patients [100]. A recent review covering several major types of cancer found no difference in the recurrence detection rates and survival when comparing nurse- and physician-led follow-up [92]. Patients living far from the hospital are more likely to more likely to drop-out of a surveillance program [102] and the distance to the hospital represent an independent significant factor of survival [103]. Nurse-led follow-up through telephone - or video consultations overcome patients travelling distances. Electronic patient reported outcome» (ePRO) is an additional method whereby patients communicate with the responsible medical staff [104,105]. The threshold of outpatient consultations must be low. Many patients can be discharged from specialist hospital-based follow-up without increasing GPs' workload. For more complex cases, additional resources may be needed to provide co- ordinated care within general practice (Reeve) [106].

Imaging

As the optimal approach to clinical follow-up remains controversial, physicians have placed high confidence in the extensive progress in imaging techniques. The reported sensitivity and specificity for computed tomography (CT) and magnetic resonance imaging (MRI) ranges in the literature. MRI has an important role in the assessment of the scull base, sinonasal cavities and nasopharynx. CT and/or MRI are indicated at the outset of observation. There is no agreement in the literature regarding choice of imaging technique for surveillance. CT or MRI is indicated in symptomatic patients and in cases where clinical assessment is not reliable [107]. In recent years 18F-fluorodeoxyglucose (FDG) combined with CT has demonstrated its superiority as it offers both anatomical and functional imaging. Today's best practice is to perform a baseline whole body FDG-PET CT scan 3-6 months for all patients after completed treatment, as this investigation accurately distinguishes persistent disease from inflammation, nonviable tumor and treatment sequelae [108]. This examination is important in predicting prognosis and avoidance of planned neck dissection in patients with initial advanced regional disease. In addition, this investigation offers the possibility of identification of local residual disease and distant metastases. Prospective randomized control trials comparing PET-CT and planned neck dissection in patients treated with radiotherapy with or without chemotherapy for N2 and N3 neck disease showed a similar 5-year survival for the two groups, but there was considerably fewer neck dissections and reduced costs in the group of patients undergoing PET-CT examination [109,110].

Opinions differ as to the length of surveillance with PET/CT. Based on both prospective and retrospective studies there is no firm evidence to support PET/CT imaging at 12 months and later posttreatment [107] and further surveillance of asymptomatic patients with PET/CT is considered a waste of resources [111], unless there are clinically suspicious findings [112]. FDG-PET/CT may be less reliable in HPV positive tumors and the optimal surveillance strategy for these tumors remains to be determined [113]. In general PET-CT has a low sensitivity for metastatic foci smaller than 5 mm and identifies fewer than half of the nodal metastases smaller than 6 mm [114]. Occult metastases and small primary tumors in the case of metastases with an unknown primary may therefore be overlooked. Furthermore, it should be noted that false positive observations are frequent [108]. Diffusion-weighted MRI, (DW-MRI) may become an effective tool, complementary to existing imaging techniques, as it allows a distinction between tumoral and non-tumoral tissue [115]. Routine imaging with conventional chest X-rays is still used but should now be abandoned as this investigation never has been associated with any survival benefit. Low- dose helical CT has become the standard investigation concerning lung metastases and primary lung cancer due to its image quality and detectability of common patterns of pulmonary [116]. The incidence of distant metastases at presentation in patients with SCCHN is generally below 5%, which is too low to warrant routine screening of all patients with SCCHN. Until there is effective systemic treatment with a curative potential, palliative treatment is the only option available for patients with distant metastases. Highly selected patients may benefit chemotherapy or immunotherapy [117-119].

Endoscopy:

Systematic biannual oesophageal endoscopy screening in 1560 patients treated for SCCHN over a period of 10 years showed 50 SCC, of which 35 % were localised to the upper third of the oesophagus. The incidence of secondary oesophageal cancer was highest for patients with initial oropharyngeal and hypopharyngeal tumors (5.7 and 2.3 % respectively) and 2.6% in patients with oral SCC. Given the short survival of these patients (median survival of 16 months), the elevated morbidity and workload, the authors found the benefit of this procedure debatable [120].

Treatment

A comprehensive presentation of treatment is outside the scope of this presentation. The history of medical treatment of primary tumors, recurrence and metastatic disease of SCCHN began in the 1970s, with single agent traditional chemotherapy. Initially, the results were disappointing. Over the years we have witnessed improvements in surgical reconstruction with free tissue transfer and better radiotherapy protocols. Early-stage SCCHN

patients receive treatment with surgery or radiotherapy alone or in combination. Most of the recurrences of these early-stage tumor are detected through symptoms the two first years after treatment [2]. In case of recurrence there are treatment options available with good long-term survival for these originally early-stage tumors [2,89]. Despite advances in treatments, 30 to 50 % of initial stage III-IV SCCHNs relapses within two years after treatment. Salvage surgery of local and regional recurrence should be considered for patients suitable for major surgery [121]. Surgery of loco-regional recurrence is commonly viewed as a double-edged sword but is nevertheless often considered the best option for many patients, although surgical treatment often has a high personal cost in terms of morbidity measured against the anticipated quantity and quality of life after surgery [121,122]. The management of primary, metastatic and recurrent HNSCC is rapidly evolving. Continued advances in concurrent systemic therapies have contributed to significant improvements in outcomes for patients with non-metastatic disease. However, this still comes with significant toxicities. Furthermore, the outcome for recurrent and metastatic HNSCC remains poor for most patients. Although immunotherapy has been able to show durable responses, this benefit is seen in only a limited number of patients. Investigational strategies using immunotherapy, vaccines, cellular therapy, and optimization of incorporation of biomarkers promise to further advance the field [123].Treatment of advanced and recurrent SCCHN has become a field for oncologists.

Prognostication

Prognostication may be defined as foreseeing an outcome (for example a procedure) based on the outcome of prior similar cases. The prognosis of head and neck cancer is determined by numerous factors related to environment, health, work, patient, tumor and treatment. Not only do we want to foresee the outcome for patients, but we also hope to better understand the biology behind SCCHN, its development, treatment response, recurrence, and outcome. The traditional role of clinical physicians regarding surveillance has for a long time been challenged by a wide range of scientists, including biologists, geneticists and pathologists, and, more recently, also mathematicians and statisticians. Almost all articles published on prognostic markers on SCCHN, whether genetic, biological, histological or histochemical, highlight some statistically significant results. With the exception of HPV positivity, there is currently no single or combination of factors that meets the required demands regarding sensitivity and specificity for a marker useful in every day clinical work. Tumor budding, defined as the presence of single cancer cells or clusters of less than five cells at the invasive front, has received considerable attention the last years [124]. Boxberg et al. [125] demonstrated an excellent intra- and inter-reader agreement in the evaluation of budding. This observation, further support the suitability of this grading system for routine pathological practice and a worthy prognostic marker of SCCHN [126]. Biologically, the aim of budding seems clear, namely, to fight themselves through the peritumoral connective tissue, to invade the host's defence and finally to invade the lymphatic and blood vessels with the consequence of local and distant metastasis. The process of tumor budding has been linked to epithelial-mesenchymal transition, which allows a polarized cell to assume a more mesenchymal phenotype with increased migratory capacity, invasiveness, resistance to apoptosis and production of extracellular matrix molecules ,The first step in tumor bud's life seems to be its detachment from the main tumor body by loss of membranous expression of adhesion [127]. The growing body of evidence support the notion that tumor budding as an aggressive and adverse prognostic factor in several types of cancer which also include SCCHN. For oral SCC carcinomas there is sufficient evidence to suggest that patients with tumors showing high-grade budding are at high risk of poor prognosis [50]. It is tempting to consider that these more or less escaped single or groups of cancer cells in fact represent the residual tumor cells left behind after local and regional surgical resection (local recidual tumor or cancer) as demonstrated by histochemistry, and responsible for a considerable number of the local recurrences. The TNM classification for prognostication for solid tumors is widely regarded as the optimal system for classifying malignant disease. Staging systems serve several purposes:

a. Prediction of the clinical course of the tumor and the prognosis for the patient, with increasing stages reflecting the severity and thus also the prognosis,

b. Choice of the most appropriate treatment,

c. Comparison of treatment results in prognostic similar groups,

d. Exchange of information between clinicians and researchers.

One of the reasons why outcomes of SCCHN seemingly have not improved significantly over the years may be explained by an imperfect TNM classification and stage grouping [128]. Previous editions of TNM classifications of head and neck cancer were almost exclusively based on empirical experience of one single dimension, the greatest superficial extent of the primary tumor. Similarly, lymph glands were classified by the greatest diameter. The latest (8th edition), of TNM classification, however, added tumor depth (with a cut-off 20 mm between early and advanced stage tumors) for oral cavity tumors and extranodal growth to the UICC and AJC classification. Remarkably, tumor volume is not accepted as a significant measure of prognosis [129]. The TNM staging can be reinforced by including non-anatomical factors such as those which are host-related (age, lifestyle, comorbidity and symptoms) and biological markers [128,130].This is exactly what research on nomograms and other mathematical modelling try to accomplish.

Mathematical modelling

Mathematical modelling has become increasingly established in medicine and holds great promise [131]. It has become progressively evident that the importance of the physician in the detection of recurrence of SCCHN is less significant than previously

thought. The medical literature contains numerous studies developing models for particular conditions (diagnostic models) or the occurrence of a certain event in the future (prognostic models) Nomograms are useful as a tool for scoring and visualization that can transform multi- factorial Cox's or competing risk models into a single score sheet. Nomograms, are used in practically all fields of cancer. Such programs allow identification of individual risks based on patient and disease characteristic for recurrence and cancer-specific and overall survival [75], benefit of adjuvant therapies and the impact of treatment on quality of life are already in use. Any variable (covariate) that may have impact on the outcome, based on prior clinical hypotheses, may be included. Nomograms are simpler and more sophisticated and with numerous advantages compared to TNM classification [73,132]. A nomogram designed for prediction of survival and local control of patients treated for laryngeal carcinoma treated by radiotherapy showed that nomograms were a significantly better prognostic predictor than TNM classification [133]. Head and neck cancers can be used as a paradigm for exploring big data applications in oncology. Computational strategies derived from big data science promise to shed new light on the molecular mechanisms driving head and neck cancer pathogenesis, identification of new prognostic and predictive factors, and discovering potential therapeutics against this highly complex disease [134].

Costs

Regular attendance at an ENT outpatient clinic and other specialist departments has significant direct and indirect costs for the patient and for society at large (van Agthoven) [135]. Comparison of costs of follow-up between clinics and countries is futile due to the great variation in global health care systems. Regular follow-up consultations after the third year are effective only regarding detection and treatment of SMTs and treatment-related complications. With adequate information, regular follow-up can be terminated at three years. Discharging patients from regular hospital-based follow-up does not mean that the patients no longer need care and provision. Increased survival and the growing number of older patients who require different kinds of care and medication will certainly increase the strain on GP's [136].

A final word

Cigarette smoking is one of most serious threats to health worldwide. Besides having a carcinogenic effect on practically all organs, cigarette smoking also leads to an innumerable number of other serious diseases. However, cancer-specific death is not affected by comorbidity [137]. It is utterly incomprehensible that the current and probably future generations are willing can continue spending vast sums of money, time and effort on treatment and research for a disease for which there is one major cause that mankind very well can manage without, namely tobacco smoking. This is not the place for further discussion on how to abandon tobacco. Nevertheless, it is encouraging to see that the number of daily smokers is declining in many countries.

Conclusion

Current proposals for surveillance advise regular physical examination under the assumption that recurrences and secondary primary tumours (SMT) are disclosed at an asymptomatic stage, which in turn give patients a favorable chance of salvage with acceptable morbidity. The evidence supporting the reliability of this surveillance protocol is relatively weak. The majority of recurrences are detected through symptoms patients' presents at regular outpatient appointments or appointments patients request in between regular appointments. The disproportionally high rate of recurrence and poor survival of SCCHN is poorly understood. It could be the aggressiveness of these tumours or absence of tools to control complete ablation of surgical excision or radiotherapy, unsuitable follow-up protocols. Almost 30 years after the significance of follow-up of patients treated for SCCHN was ascertained there is no unanimous consensus on the optimum posttreatment surveillance of patients treated for SCCHN. Current surveillance protocols are still entirely based on assumptions and tradition, not evidence. A generally accepted follow-up protocol is a matter of great concern, considering the number of lives at stake the immense workload and expenditure of treatment and surveillance of this group of cancer patients. A 'one size fits all' surveillance protocol is recommended by several national head and neck societies, but these protocols do not take into account differences in behaviour according to the site and stage of the primary tumors. A more patient-focused individualized post-treatment follow-up policy based on already known unfavourable variables is required. This problem was solved by introducing nomograms. Such programs present individualised prognostication far more applicable than conventional TNM classification that for long has been considered the gold standard for prognostication. Furthermore, ongoing studies using big data to decide (BD2D) are in progress. It is expected that far more data will be available for personalized treatment decision and to foresee recurrence and survival.

The prevalence of symptomatic recurrence in SCCHN is well supported, but solid proof of a survival benefit of symptomatic recurrence is still limited. Information at discharge and follow-up consultations may be inadequate, difficult to understand or soon forgotten. Several authors emphasise the need for education, i.e., easily accessible and adequate description of symptoms and complaints that might signify recurrence and the severe repercussions of not seeking immediate advice. Having this information patients may feel more secure and observant with regard to his/her own welfare and better prepared for timely report of any worries. Physician-led follow-up is time consuming and costly. Much of this work can safely be performed through regular telephone or video interviews or other ways digital communication by nurse specialists. Despite advances in treatments, 30-50% of patients treated with curative intent for stage III- IV disease experience relapse within two years after treatment. The prognosis of recurrence of early-stage tumors is very good, but poor for

advanced tumors. A significant number of recurrences may be explained by growth of tumor cells left behind after surgery and further deterioration of premalignant manifestations in the mucosa at or close to the site of resection. Needless to say, prevention is always better and less costly than treatment. In this connection we want to stress these premalignant mucosal changes should be targeted as intensively as genuine tumors. Any SCC occurring > 3 cm from the original tumor or occurring> 3 years after treatment of the original tumor should be considered a second malignant or second field tumor. The majority of recurrences of SCCHN are detected through symptoms patients present at planned follow-up appointments or patient self-initiated consultations. This illustrates that symptomatic recurrence should receive more attention. One factor that might explain delay in recurrence detection and treatment is patients lacking knowledge regarding symptoms that might alert recurrence. Information at discharge and follow-up consultations may be inadequate, difficult to understand or soon forgotten. The key issue is education, namely, adequate and easily accessible information regarding symptoms and complaints that might signify recurrence and the severe repercussions of not seeking immediate advice. As no formal list of potentially ominous symptoms and signs that might signify recurrence exists, clinics or national head and neck cancer societies are urged to prepare leaflets that in lay language describe red flag symptoms and signs of recurrence.

These end of treatment letters should be handed over to patients and/or the closest next of kin on discharge, should also provide information on SMTs, treatment-related side effects and complications, as well as possible alterations in patients' quality of life and where to seek help. Such information should also be easily available on digital platforms. Such information becomes even more important considering the aging population in western countries. When properly informed it seems likely that patient feel more secure and observant about their health status. To date, there is only inadequate information regarding advantageous survival of symptomatic recurrence. When systematically incorporated, we suppose that symptomatic recurrence may increase recurrence detection and thus give more patients a chance of secondary treatment. Recurrence at the primary site is probably the most important reason for recurrence. Residual tumor cells following surgery and remaining premalignant epithelial changes are probably the most important cause of local failure. The application of frozen sections has several drawbacks and ought to be replaced by safer methods for assuring clean resection margins. There are several ingenious methods have been invented for this purpose and also for detection of premalignant epithelial changes intraoperatively or later. There are several ways to improve today's surveillance protocol, increasing efficacy and reducing costs without jeopardizing the quality of follow-up. As physicians must realize that other fields of research may provide tools and that exceed and to some degree replace clinical examination. There is a strong need for rethinking of today's follow-up of patients treated for SCCHN.

Conflict of Interest: None.

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