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### Cooperation as core value in an innovative era

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## EDITORIAL

# Cooperation as core value in an innovative era

Diagnosis, treatment, and rehabilitation of patients suffering from oral cancer are shared responsibilities of primary care givers like dentists, physicians and oral medicine specialists, and intramural secondary care specialties. Because of the complex nature of treatment and the necessity of long-term care in most patients, the treatment and follow-up of head and neck cancer patients are confined to centers with dedicated teams in most countries.

Early referral of patients suspected for oral cancer is considered important because survival is related to tumor stage and primary care givers play a pivotal role in that respect (Grafton-Clarke et al., 2019). Where health care is organized with possibilities of a quick and easy referral, the risk of delayed referral is greatly reduced. The interval between observation of a suspect lesion in the head and neck area and referral increases when healthcare practitioners are poorly trained in recognizing early signs or try several interventions before referral (Figure 1). For instance, in a survey focused on oral cancer knowledge primary care givers did regularly perform oral examinations, but they failed to identify at which sites cancer typically occurs (Applebaum et al., 2009). Specifically, a correct identification of oral leukoplakia, currently renamed by the World Health Organization as “potential malignant disorders,” is an important factor of early referral. Globally the policy is that patients who have a red (erythroplakia) or red and white (erythroleukoplakia) or white (leukoplakia) patch in their oral cavity should be sent for assessment of possible oral cancer within 2 weeks after such a lesion has been observed by a primary care giver. As mentioned before, early referral is considered important despite the fact that scientific studies find that diagnostic delay is a moderate risk factor of mortality from head and neck cancer (Seoane et al., 2016; Seoane et al., 2012). This moderate risk, however, does not imply that the two week rule is not valid. This two week term remains a practical guide for primary care givers to act upon.

The incidence of oral cancer is increasing as a result of continued smoking, aging population, and to a lesser extent the spread of HPV infections. In Europe, data show that the incidence of oral cancer is increasing as well as the prevalence (Figure 2). The 10-year prevalence, described as the number of the population that is diagnosed with oral cancer and still alive after treatment, is increasing as a result of the increase in both incidence and survival. Thus, the burden of oral cancer on the society is increasing (Bravi et al., 2020). In the last decade, attempts have been made to raise the awareness of the general public on oral cancer by campaigns such as the “word of mouth” program. The public is advised to self-exam their oral cavity for suspicious sores and feel the neck for lumps. Oral cancer screening to date has not been implemented in most countries and most

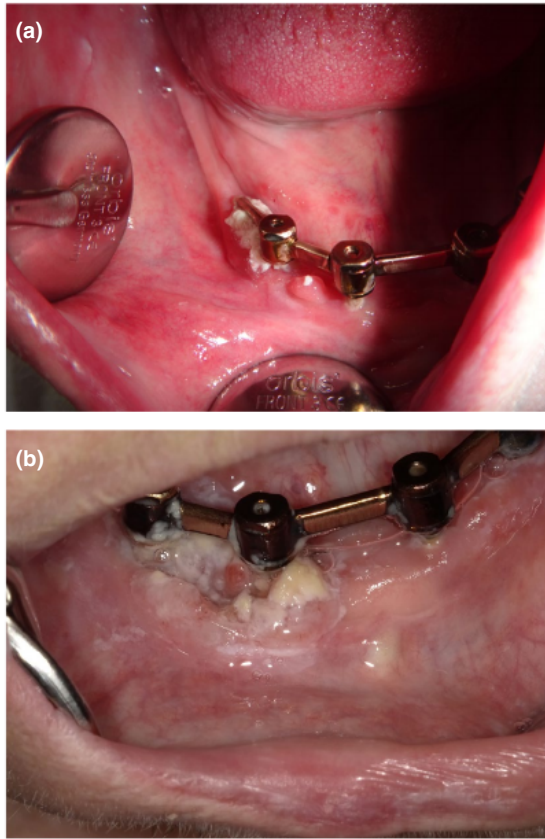
likely will not be introduced at all due to insufficient effect and costs. An oral cancer screening program might not be necessary if people visit a dentist regularly.

Surgery is the mainstay of the treatment of oral cancer and most likely will continue to be the coming decade despite potential paradigm shifts in treatment strategies. Future therapeutic approaches will be shaped by the introduction of new drugs like immunotherapy. But instead of taking over, new therapeutic options most likely will be supportive in the treatment of oral cancer, building on existing ones. For example, current trials focus on neoadjuvant treatment with immunotherapy to reduce high stage tumors in size with hopefully a less extensive surgery as a result (Stafford & Kaczmar, 2020). One or two preoperative gifts of immunotherapy already show favorable results in terms of reduction of tumor size, but it is yet too early to conclude that it would improve survival. Even when immunotherapy proves to be effective in the neoadjuvant setting, the primary treatment of resectable tumors most likely will remain to be by surgery. Therefore, it continues to be relevant to develop new as well as to refine existing surgical strategies of oral cancer. Issues like improving survival, quality of life, and rehabilitation remain relevant. There is a continuous need for developments!

The current issue of Oral Diseases contains contributions that address some of the challenges in Head & Neck Oncology. One of the issues under debate is the necessity of a 5 mm width of the surgical margin (Aaboubout et al., 2020). It is clear that local control is best achieved when at least a margin of 5mm is obtained. Surgeons agree that this should be the objective of surgical procedures. A margin of less than 1 mm is considered a high risk of recurrence and conversely, margins larger than 5 mm are considered low risk of recurrence. The debate concerns a margin between 1 and 5 mm. Somewhere between 1 and 5 mm, the risk of local recurrence reduces from high to an intermediate to a low risk. A challenge for future research is to assess whether postoperative policies can be refined when combining margin width with the biological behavior of a tumor. Some authors suggest that when a margin <5 mm is obtained in surgical removal of early stage oral cancer (T1), adjuvant treatment may not be needed when there are no signs of aggressive growth patterns (invasive front, peri-neural growth, lymph-vascular invasion) (Jang et al., 2017). Rigorous scientific studies are needed to test this concept because recurrences can be difficult to treat. Salvage treatment of recurrences is a challenge to oncologists and a burden for the patient (van Weert & Leemans, 2020).

Frustrating for head and neck surgeons is the lack of easy applicable technology that can support them in decision making in the

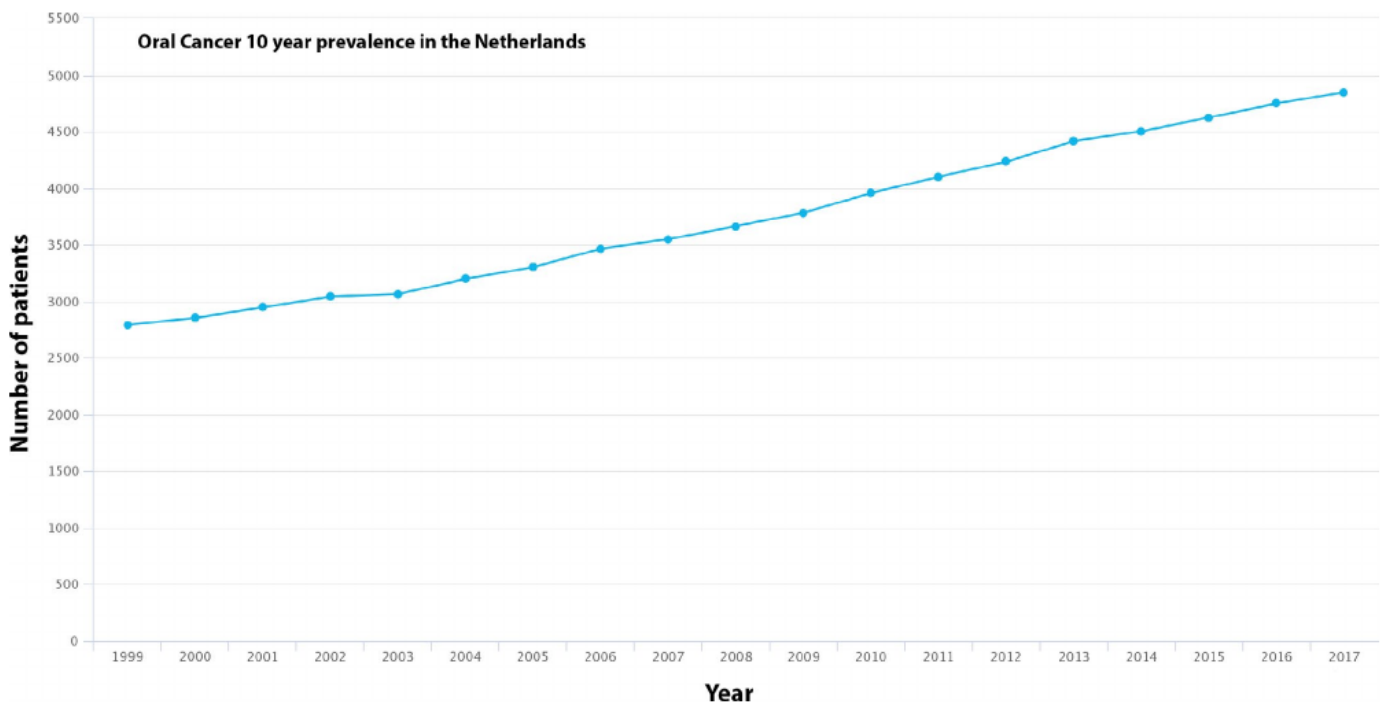




**FIGURE 1** Example of a late recognized oral lesion. This lesion was initially treated as an implant-related infection (a) but in fact was a leukoplakia that developed into squamous cell carcinoma (b)

operating room with regard to the width of the soft tissue margin. To date, only frozen sections taken from the tumor specimen are accepted as an intra-operative means for margin analysis. Several new/emerging technologies are currently studied for intra-operative soft tissue margin assessment (Vonk et al., 2020). Much attention in the literature is paid to optical techniques. Intra-oral ultrasound, and spectroscopic techniques such as raman and fluorescence imaging using molecular targets are increasingly reported as potential solutions for intra-operative margin assessment. Which technique will be incorporated as a reliable tool remains to be answered with scientific studies, but it is likely that in the coming decade surgeons will be supported in intra-operative decision making by an approved technology. The intra-operative planning of bone margins is nowadays often routinely supported by 3D technology (Kraeima et al., 2020; Merema et al., 2020; Merema et al., 2020). For example, 3D-printed cutting guides or navigational devices allow for a highly accurate execution of bone cuts. 3D technology is used by many head & neck centers and it can be considered as an example of successful implementation of new technology in the operating room.

The benefit of cooperation between primary and secondary caregivers in Head & Neck Oncology is best shown in the process of treatment planning. Planning often involves removal or treatment of foci and rehabilitation planning after surgical procedures (Spijkervet et al., 2020). Ideally, before surgery the plan for rehabilitation is defined and integrated with the surgical treatment (Alberga et al., 2020; Vosselman et al., 2020). In this perspective, the past three decades the success of placing dental implants has been established. Implant-retained prosthodontics are now a cornerstone of



**FIGURE 2** Ten-year prevalence of oral cancer in the Netherlands. The graph displays the patients diagnosed with and alive after treatment of oral cancer. Each data point shows the 10-year prevalence (source: Netherlands Comprehensive Cancer Organisation, <https://www.iknl.nl/nkr-cijfers>)



dental rehabilitation after oncological surgery. Several practical issues remain to be resolved, however, such as the timing of placement of dental implants as well as the placement of dental implants in free flaps. Like for surgical planning, planning of an oral rehabilitation is supported by 3D technology. This technology supports precise placement of implants and design of prosthetic devices. Notwithstanding the long experience with dental implants, new ideas based on implant technology still emerge and become implemented in clinical practice. The application of zygoma implants after maxillectomy in combination with soft tissue flaps is an example of a creative idea finding its way into the clinic (Hackett et al., 2020).

Treatment of cancer in the head and neck area is commonly accompanied by damage to the salivary glands (Barazzuol et al., 2020; Vissink et al., 2015). Damage to the salivary glands is unavoidable as the salivary glands are located superficially and the ionizing radiation has to pass salivary gland tissue to reach the tumor. While there is many approach to minimize this radiation damage to salivary gland tissue, there is yet no satisfactory therapy to treat radiation-induced salivary gland damage. A feasible option might be harvesting salivary gland tissue during, for example, a head and neck dissection procedure, isolate and proliferate stem cells from this tissue and return these stem cells to the salivary glands that are damaged by the postoperative radiotherapy. Such stem cell therapy is an attractive option for the long-term treatment of hyposalivation related xerostomia induced by irradiation, but is in need of further study in animals and preliminary studies in human before it can evolve into a clinically applicable method. Future studies should also focus on a better understanding of the radiosensitivity of parotid and submandibular salivary gland tissue (Serrano Martinez et al., 2020).

All these developments show the benefits for patients of a good cooperation between primary and secondary caregivers. The good cooperation also demonstrates what can be achieved if efforts are focused and put into practice.

## KEYWORDS

dental implants, diagnosis, head and neck cancer, head and neck oncology, head and neck surgery, incidence, planning, prosthodontics

## CONFLICT OF INTEREST



None to declare.

## AUTHOR CONTRIBUTIONS

**Max Witjes:** Conceptualization; Writing-original draft; Writing-review & editing. **Arjan Vissink:** Conceptualization; Writing-review & editing.

## PEER REVIEW

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