

Implications of Chemotherapy, Radiation Therapy, and Surgical Treatment in Oral Cancer

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ABSTRACT

Oral cancer includes both the cancers of the mouth and back of the throat. This literature review investigates viable treatment modalities for adult patients diagnosed with oral cancer including the comparison of chemo/radiation therapy, surgery, and new treatment modalities. Surgical interventions are often the initial treatment, depending on tumor characteristics, and may require reconstructive procedures. Chemotherapy and radiation therapy, while effective, present challenges such as side effects such as nausea, vomiting, hair loss, and fatigue. With surgery, there is the consideration of different types of therapies. Post-operative care, lifestyle implications, and treatment success vary among these modalities. New treatments such as gene therapy and immunotherapy are also starting to appear. Findings suggest the drawbacks and the advantages of different treatments and possible preventive measures.

Introduction

Overall, 11.5 adults per 100,000 will develop oral cancer with the incidence rates significantly higher for males than females. The incidence of oral cancer increases with age, with the increase becoming more rapid after age 50, particularly for adults aged 65 years and older. Approximately 4% of all cancers are of the oral cavity or oropharyngeal, according to Nandini et al., 2020. In adult patients diagnosed with oral cancer, there are a variety of treatment management options that can be used to either remove the cancer or prevent the cancer from metastasizing. These include: chemotherapy or radiation therapy, surgical treatments, gene therapy, and immunotherapy, all of which have implications for post-operative care, lifestyle, and overall well-being. Each treatment option presents unique considerations and potential benefits for patients.

Oral cancer refers to a multitude of cancers like squamous cell carcinoma, lymphoma, sarcomas, or melanomas. It ranks as the sixth most prevalent cancer globally and while tobacco and alcohol consumption are the primary contributing factors, recent studies have linked Human Papillomavirus to oral cancer as well (1). Oral cancer primarily affects the lip, oral cavity, and oropharynx. The process of detecting oral cancer, known as screening, involves a systematic approach that is aimed at identifying the disease in its early stages, before symptoms manifest (2). Symptoms typically develop later, after the cancer is already at moderately advanced stages. The clinical signs and symptoms of head and neck tumors are often nonspecific and can be misleading, resembling symptoms of other common illnesses (3). Tumors in the oral cavity are observed as white, red, or speckled lesions on the oral mucosa. However, approximately 50% of patients with oral cancer are diagnosed at an advanced stage, where the lesions may appear mature, with central ulceration and indistinct borders (3). Pain is the most frequent presentation and the tongue and the floor of the mouth have the highest occurrence (4). In its initial stages, an abnormal patch of red and white tissue, also known as erythroplakia, is found. However, in the advanced stages, there are rigid ulcers and lumps with irregular margins (4). Oral cancer can be found in various locations within the oral cavity. While it may appear in any area, there are certain locations where it is more commonly found. In Western countries, the most frequently affected sites include the tongue and the floor of the mouth due to smoking and alcohol consumption. Together these account for over 50% of

cases, but other areas including the buccal mucosa, retromolar area, gingiva, and soft palate are also commonly involved. Oral cancer may also affect the back of the tongue and the hard palate (4).

Surgery plays a crucial role in the treatment of oral cancer and is often the first treatment. The choice of surgical approach depends on several factors, including the tumor characteristics, the primary site, location, size, proximity to bone, and depth of infiltration (5). Surgery is often used for small, early-stage cancers that have not spread. After the cancer is removed, reconstructive surgery can help restore the appearance and function of the areas affected by the cancer or cancer treatments (6). Although chemotherapy is most used to treat cancer that has spread beyond the primary site, it may also be used in combination with surgery to shrink tumors before they are removed or to kill any remaining cancer cells after surgery.

Chemotherapy and radiotherapy are two common treatment modalities used to treat a variety of cancers and can be used alone or in combination with other treatments, such as surgery or immunotherapy, depending on the type and stage of the cancer. Chemotherapy involves the use of powerful drugs to kill cancer cells and is administered orally or intravenously. Chemotherapy works by targeting fast-growing cancer cells, but it can also affect healthy cells in the body, leading to side effects such as nausea, vomiting, hair loss, and fatigue. Common ways chemotherapy is given include oral medications such as pills or capsules given to a patient to swallow (7). Some of the current chemotherapeutic drugs used to treat oral cancer are cisplatin, 5-Fluorouracil, tegafur/uracil, paclitaxel, carboplatin, and calcium folinate which are all usually taken orally to improve compliance with the patients. Some chemo drugs cause long-term side effects, like heart or nerve damage or fertility problems (8). Contraindications for chemotherapy may include: patients with pre-existing bone marrow suppression, patients with severe liver or kidney dysfunction, patients with severe infections or low white blood cell counts, pregnant women or women who are breastfeeding, and patients with a history of certain medical conditions, such as heart disease or lung disease.

Radiation therapy, another treatment modality, is a targeted approach to eliminate cancer cells by causing DNA damage which prevents cell repair and leads to destruction. Radiation therapy does not kill cancer cells right away, as it takes days or weeks of treatment before the DNA is damaged enough for cancer cells to die and at high doses it kills cancer cells or slows their growth (7). Cancer cells whose DNA is damaged beyond repair, stop dividing or die and when the damaged cells die, they are broken down and removed by the body. The usual method of radiation therapy uses high-energy photons to kill cancer cells, but it can also affect normal cells such as hair, salivary glands, and mucosa. Radiation therapy drugs are used to enhance its effects or to manage side effects. Radiosensitizers are drugs given before radiation therapy to increase the sensitivity of cancer cells to radiation. This includes cetuximab, fluorouracil, and cisplatin. These medications are used to enhance the effectiveness of radiation by destroying cancer cells (9). Contraindications for radiation therapy may include: patients who are pregnant, patients with certain autoimmune diseases or connective tissue disorders, patients with a history of radiation therapy to the same area, and patients with certain types of cancer that are not responsive to radiation therapy. Chemotherapy and radiation therapy can go hand in hand; the combination of them can target both the primary tumor and any potential microscopic cancer cells in the surrounding area, reducing the risk of local recurrence.

Methods

This scoping review focused on the following question:

In adult patients diagnosed with oral cancer, how do chemo/radiation therapy treatment options affect post-operative care, lifestyle, and other implications in comparison to surgical treatments?

The definitions of population, intervention, comparison, and outcome (PICOs) were developed based on the focused question as follows:

Population- Adult patients diagnosed with oral cancer

Intervention- Chemotherapy and radiation therapy

Comparison- Surgical treatment of oral cancer
Outcome- Post-operative lifestyle and success of treating cancer

Search Strategies

An electronic search without time or language restrictions was conducted using Pubmed, Google Scholar, and other databases of published research articles. The reference lists of included studies and relevant reviews were also searched for other potential studies. The detailed search strategies were as follows: #1: Chemotherapy AND lifestyle, #2 Chemotherapy Drugs, #3 Radiotherapy AND Chemotherapy, #4 Surgery AND Oral Cancer, #5 Radiotherapy AND Oral Cancer, #6 Causes of Oral Cancer, #7 Oral Cancer AND Chemotherapy, #8 Chemotherapy Complications

Discussion

After undergoing surgery, many patients may require reconstructive surgery and rehabilitation to maintain both function and appearance. Rehabilitation professionals such as speech therapists, swallow therapists, physical therapists, and occupational therapists help patients maintain an acceptable quality of life post-surgery activities to improve the functioning and independence of the patient. In a nationwide cohort study of 173,643 patients who underwent general surgery, operations performed urgently had a 12.3% rate of morbidity and 2.3% rate of mortality, which were different from the emergency and elective surgery according to Mullen et al.(10). With surgery, there can be compromising aesthetic results such as when structures are removed with oral cancers. Glossectomy is the surgical removal of part of the tongue mainly used for tongue cancer. While most patients can still speak, their speech may not be clear after getting a glossectomy and the tongue's ability to swallow may also be affected, but speech therapy can often help with this (11). There is also facial bone structure removal which postoperative can have a significant effect on facial aesthetics.

Oral chemotherapy has convenience and ease of administration as the treatment can be taken at home, reducing the need for frequent hospital visits, and minimizing disruption to the patient's daily life. One example of a powerful chemotherapy drug is 5-fluorouracil (5-FU) which is highly schedule-dependent, meaning its effectiveness is closely tied to the specific dosing schedules. 5-FU's oral administration can be challenging due to issues like absorption and the potential for causing diarrhea. Therefore, various approaches have been made to combat the lack of reliability of 5-FU's oral administration such as developing pro-drugs like capecitabine which can break down 5-FU. Capecitabine has shown success as an oral chemotherapy option in breast and colorectal cancers as it achieves better response rates while maintaining similar progress and overall survival times compared to 5-FU. Another powerful drug used in chemotherapy is the combination of cisplatin and 5-FU. The combination of both cisplatin and 5-fluorouracil, given over a 120-hour infusion, has been found to be an effective treatment for squamous cell head and neck tumors. Several phase II studies by Andreadis et al. have shown that this combination has produced response rates ranging from 20% to 70%, with complete response rates ranging from 0% to 27% (12). Furthermore, in a randomized study compared the combination with either cisplatin or infusional fluorouracil alone and found that the overall response rate and time to disease progression were better with the combined drugs. After 9 months of follow-up, 40% of patients treated with the combination were alive, compared with 24% of patients treated with cisplatin and 27% of patients treated with fluorouracil alone (12).

Radiotherapy uses high-energy photons to kill cancer cells but this leads to damage of hair, salivary glands, and mucosa. The standard of care for head and neck squamous cell carcinoma includes radiotherapy with the treatment of weekly 100 mg/m² of cisplatin (13). However, this is associated with severe toxicities with devastating effects on patients. Alternatives like weekly 40 mg/m² have been used in an attempt to reduce toxicities. In a study, 52 patients had their data obtained from the Patients' Database of St. James Hospital,

Dublin. The median age of the study cohort was 54 years (range 33-73). Of the patients, 40 (76.9 %) were male and 12 (20.1 %) were female. The primary tumor sites were, the oral cavity and oropharynx in 38 (73 %), larynx in 10 (19 %), and hypopharynx in 4 (8 %). In total, 33 (63.5 %) patients had stage IV disease, while 19 (36.5 %) had stage III disease. The treatment was definitive in 35 (67 %) patients and adjuvant in 17 (35 %). Full-dose radiotherapy was achieved in 50 (96 %) patients. A total dose of 200 mg/m² or more was reached in 37 (71 %) patients. The effects included grades 3 and 4 mucositis, which occurred in 22 (43.3 %) and 6 patients (12 %). Grade 3 and 4 neutropenia in six (11.5 %) and three (5.7 %) patients, grade 3 anaemia in 20 (38.4 %) patients, and grade 2 renal toxicity among the study cohort, was observed in six (11.5 %) patients, and death occurred in one patient (13). This study shows that weekly cisplatin is associated with moderate to severe toxicities and might lead to suboptimal chemotherapy delivery. For radiation therapy without health care, it costs approximately \$10-50,000. The average cost of gene therapy is \$1.5 million while immunotherapy with drugs is around \$200,000 (14).

Treatment modalities for other types of cancers related to oral cancer such as head and neck cancer include targeted therapy, immunotherapy, and gene therapy. The most promising targeted therapies include DNA damage response inhibitors and immune checkpoint inhibitors (15). Targeted therapy is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread; most targeted therapies are small-molecule drugs or monoclonal antibodies. Immunotherapy is a treatment method for head and neck cancer patients and is a type of cancer treatment that helps a patient's immune system fight cancer by detecting and destroying abnormal cells. It can boost or change how the immune system works to find and attack cancer cells and may be used in combination with surgery to help prevent the cancer from coming back (16). Gene therapy is gene editing and silencing where the RNA interface can be used in different ways to treat cancers but it does have its downfalls as there are high chances for the development of resistance and therapeutic failure (15). As early as the 1960s, scientists speculated that DNA sequences could be introduced into patients' cells to cure genetic disorders, one prime example being, in 1990, 4-year-old Ashanthi de Silva became the first gene therapy success (17).

Conclusion

Despite the vast treatment modalities available for oral cancer, the choice of treatment can have profound effects on lifestyle and post-operative care. Surgery aims to remove the tumor while preserving functionality and aesthetics, yet it can result in significant facial and functional changes. However, aesthetic consequences and functional limitations are often associated with procedures like glossectomy, and facial bone structure removal, but with time lifestyle is affected if the patient must adapt to altered abilities. In contrast, chemo/radiation therapies offer alternatives, especially for advanced cases, but do include side effects and financial burdens. But there is also the convenience of home-based oral chemotherapy, which comes with schedule-dependent drug administration and potential side effects, such as mucositis and myelosuppression. Further research includes more preventative diagnosing methods and imaging in order to avoid treatment altogether.

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