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GUIDELINE

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CACA guidelines for ultrasound hyperthermia for oral and maxillofacial head and neck squamous cell carcinoma

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Abstract

Most of the patients with oral and maxillofacial malignancy are in the middle and advanced stages at diagnosis and the incidence rate is increasing in recent years. Chemotherapy alone is difficult to benefit the survival of patients with advanced oral and maxillofacial malignancy. Ultrasound hyperthermia is a new and effective treatment for malignant tumor, which is developing rapidly in addition to conventional treatment. However, at present, ultrasound hyperthermia has not been widely used in the treatment of oral and maxillofacial malignancy. Therefore, formation of a guideline on ultrasound hyperthermia for oral and maxillofacial malignancy is mandatory, in order to promote and standardize the clinical practice of ultrasound hyperthermia in this field, and improve the long-term survival rate and quality of life of patients.

Keywords Oral and maxillofacial malignancy, Ultrasound hyperthermia, Combination therapy, Cavitation effect, Guideline

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Oral cancer included cancers of the mucosa occurring in the buccal, floor of the mouth, anterior 2/3 of the tongue, gingiva, posterior triangle of the molar teeth, and hard palate area, and squamous cell carcinoma is the most common subtype [1, 2]. In recent years, the incidence of oral squamous cell carcinoma has been increasing year by year, and most patients diagnosed are in the middle and late stages of malignancy. Patients with advanced tumors often cause facial disfigurement and dysfunction, and the quality of survival is significantly reduced, and most miss the timing of surgery. With the gradual development of integrated therapies such as surgery, radiotherapy, chemotherapy and biotherapy for advanced oral cancer, the quality of life of patients has been significantly improved, although the long-term efficacy has not been substantially improved [3]. Therefore, various integrative therapies have been increasingly emphasized in the treatment of advanced malignancies.

However, chemotherapy alone provides limited benefit in advanced oral and maxillofacial head and neck tumors. A single-center study of 256 cases of primary advanced oral cancer in China showed that TPF regimen (docetaxel 75 mg/m2 d1, cisplatin 75 mg/m2 d1, fluorouracil 750 mg/m2 d1-5, once every three weeks for two cycles) induction chemotherapy only improved the overall survival and disease-free survival of patients with locally advanced oral squamous carcinoma who were treated effectively [4]. Therefore, how to improve the response rate of induction chemotherapy is an important way to improve the overall outcome of advanced oral cancer. Hyperthermia is a fast-developing technique with a high safety profile, and is considered a new effective treatment for malignant tumors after surgical treatment, radiotherapy, chemotherapy and biologically targeted therapy. Hyperthermia has demonstrated better efficacy in a variety of solid tumors and can significantly improve the near-term outcome and long-term survival rate of patients; at the same time, hyperthermia can effectively increase the killing power of chemotherapeutic drugs on tumor cells and promote apoptosis of tumor cells, so that some patients with advanced squamous carcinoma of the oral and maxillofacial region who are not clinically indicated for surgery can regain the indication for surgery and improve the quality of survival [5].

Ultrasound is one of the fastest growing and increasingly valued heating technologies, and countries are competing to study the relevant techniques and equipment, and there have been reports of its application to the clinic [6]. However, ultrasound hyperthermia is still far from popular in the field of oral and maxillofacial head and neck tumors, and there is no guideline or clinical application guidelines for ultrasound hyperthermia including oral squamous carcinoma. Therefore, it is of great clinical significance to develop an guideline on ultrasound hyperthermia for oral and maxillofacial head and neck tumors in a timely manner. In view of this, based on the research results of ultrasound hyperthermia at home and abroad, and taking into account the current medical situation in China, the Special Committee on Integrative Medicine for Oral and Maxillofacial Tumors of China Anti-Cancer Association organized relevant experts to discuss and formulate the "Guideline on Clinical Application of Ultrasound Hyperthermia for Squamous Oral and Maxillofacial Head and Neck Cancers", aiming to promote and standardize the clinical practice of ultrasound hyperthermia in this field. The aim is to promote and standardize the clinical practice of ultrasound hyperthermia in this field for the benefit of patients with oral and maxillofacial malignancies.

1 Mechanism of ultrasound hyperthermia

Hyperthermia therapy (HT) is a method to kill tumor cells by selectively heating the tumor to the therapeutic temperature (40–44 °C) through a physical heating device. Compared with other heating methods such as microwave and radiofrequency, ultrasound has many advantages such as good directivity, strong penetration, and no electromagnetic radiation, while it is easy to achieve uniform heating of tumor tissues [7, 8]. In addition, ultrasound hyperthermia technology has certain intrinsic characteristics that can design the thermal field pattern according to the shape and extent of the treatment area, so that the target area can be uniformly heated, and the temperature can be accurately measured [9]. Therefore, ultrasound hyperthermia can effectively treat surface and superficial oral and maxillofacial tumors without electromagnetic interference and reflection during the treatment process, and it is convenient for temperature measurement by probes.

The anti-cancer mechanism of ultrasound hyperthermia includes the following aspects (Fig. 1): ① Direct cytotoxic effect of heat. Warm heat (42 ± 1℃) can act on cell membrane, cytoskeleton system (ribosome, lysosome, rough endoplasmic reticulum, etc.) to increase the permeability of cells, followed by inactivation of some enzymes related to cell metabolism, and finally cause apoptosis. This effect is especially obvious for cells in hypoxic, malnourished and low pH environments. Due to the specificity of tissue structure, cells within the tumor are often in this microenvironment and therefore are also more sensitive to heat, making heat therapy selectively antitumor. ② Synergistic antitumor effect with radiotherapy. 1) Sensitizing effect, in addition to preventing tumor cells from repairing various damages caused by radiation and chemical drugs, heat therapy can also release tumor cells from resistance to radiotherapy + chemotherapy. It

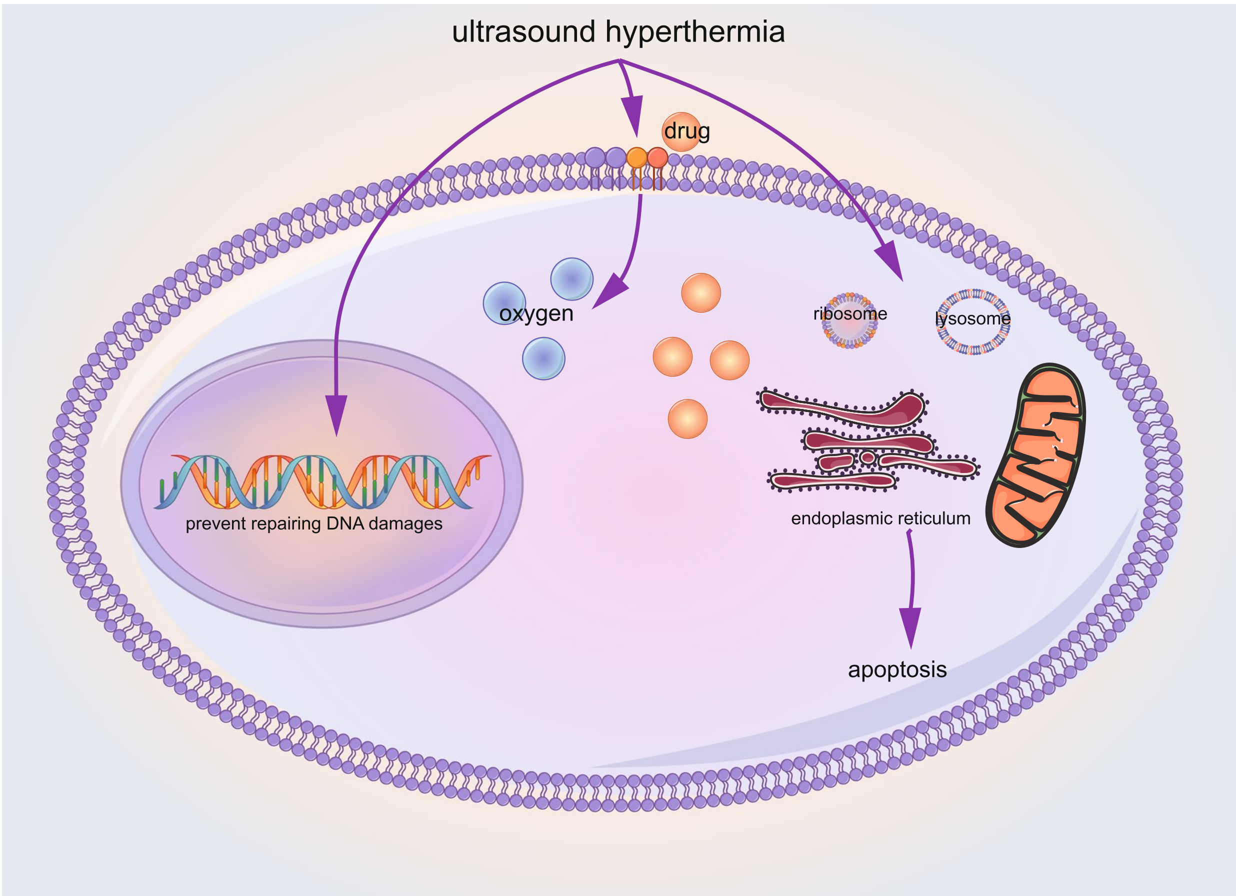

Fig. 1 The anti-cancer regulation mechanism of ultrasound hyperthermia

is generally believed that by increasing the partial pressure of oxygen in tissues, oxygen-depleted cells that are not sensitive to radiotherapy become sensitive to radiation, and by changing the permeability of cell membranes to improve drug absorption and alter drug metabolism, etc., the cytotoxic effect of chemotherapy drugs can be improved, so that certain chemotherapy drug-resistant tumor cells become sensitive to drugs. 2) Complementary effect, when heat therapy is applied, only effective temperature and sufficient time can be achieved to kill the tumor cells. Due to the heterogeneity of body tissues and abnormal blood circulation in tumor tissues, it is difficult to heat the tumor evenly, especially the peripheral area often cannot reach the treatment temperature. The tumor cells in the central area of the tumor are not sensitive to radiotherapy due to lack of oxygen and hypotrophy; similarly, in chemotherapy, the drugs can easily reach and act on the peripheral area of the tumor but not easily penetrate to the central part. Conversely, the local fibrosis and blood flow disorders of the tumor caused by radiotherapy aggravate the tumor hypoxia, low pH and hypotrophy, and increase the thermal sensitivity of tumor cells in this microenvironment. In addition, in terms of the temporal phase of the cell proliferation cycle, M-phase cells are the most sensitive to radiation and S-phase cells mostly show resistance to radiation; and warmth has the strongest killing effect on S-phase cells [10]. All of these indicate that heat therapy has multiple complementary advantages and the rationality of combined application with chemotherapy and radiotherapy.

When the sound intensity of ultrasound is low, the warm-heat effect is dominant; at high sound intensity, the instantaneous cavitation effect is dominant. Within a certain range, as the sound intensity increases, the mechanical effect and cavitation effect also increase. Therefore, the therapeutic effect of ultrasound hyperthermia on tumor can be stronger than that of simple heating treatment. The reason is that ultrasound is a form of fluctuation and its vibration can cause biological macromolecules, cells and tissue structures to be in an intense mechanical field of motion, thus causing changes in their structure and function. Ultrasound is also a form of energy, due to vibration and temperature rise, causing cell membrane damage or enhancing lysosomal activity and protein damage, thus causing cell death. Due to the presence of tiny bubbles in the tissue, ultrasound can cause temperature rise in and around the tiny bubbles, and the oxygen radicals generated as well as the high-speed microthermal flow cause serious damage or even destruction to the cells [11, 12]. Therefore, in addition to thermal effects, there are multiple therapeutic effects during ultrasound hyperthermia, and its killing effect on tumor cells is the result of multiple effects together.

Ultrasound hyperthermia is a non-invasive, minimally invasive and highly effective physiotherapy technique that uses the characteristics of biological tissues to absorb ultrasound energy to increase their own temperature, which can kill lesioned tissues by high temperature or induce recovery by low temperature. Bai et al. found that tumor ultrasound hyperthermia can directly kill tumor cells; it can also decrease mitochondrial membrane potential and destroy cell membrane integrity, thus inducing and accelerate tumor cell apoptosis; inhibit angiogenesis in tumor, which in turn decreases tumor T-stage and shrinks tumor [13]. Local heat therapy can increase blood circulation and enhance cell membrane permeability, which increases the concentration of local chemotherapeutic drugs and further enhances the effect of chemotherapy. In addition, Wang et al. confirmed that TRIF-NF-γB pathway was significantly inhibited in oral squamous carcinoma cells treated with ultrasound hyperthermia at 42 ℃ for 30–60 min. [14] Ju et al. found that ultrasound hyperthermia had a chemosensitizing effect on oral squamous carcinoma cells in vitro. Ju et al. also observed that chemotherapeutic drugs exerted highest inhibition effect on tumor cells when the heating temperature increased to 42 ℃ and the duration heating-time reached 45 min [15, 16]. All these results indicate that ultrasound hyperthermia could sensitize chemotherapy, and ultrasound hyperthermia has a positive role in the comprehensive treatment of malignant tumors.

The palliative effect of ultrasound hyperthermia on advanced tumors should not be neglected either, especially the effect on cancer pain relief. Pain affects the eating, sleeping and mental status of patients with advanced malignant tumors to varying degrees, which seriously reduces the quality of life of patients, and sometimes it is not relieved even with pharmacological analgesic treatment. After the treatment, the pain was significantly relieved. The mechanism of the palliative effect of heat therapy is still unclear and needs further study.

2 Clinical rationale for ultrasound hyperthermia for oral and maxillofacial head and neck tumors

Amichetti et al. used a preoperative hyperthermia regimen including: cisplatin 20 mg/m2/w + hyperthermia 42.5 °C/30 min + radiotherapy 2 Gy × 5 × 7 weeks in 18 patients with advanced head and neck squamous carcinoma and achieved a remission rate of 88.8%, including complete response (CR) rate of 66.6% [17]. Nagashima et al. applied hyperthermia to treat patients with advanced head and neck squamous carcinoma and compared the efficacy with that of patients with advanced head and neck squamous carcinoma treated with radiotherapy alone, and showed that hyperthermia had significant advantages in terms of overall remission rate, CR rate, and long-term survival [18], indicating that hyperthermia not only improves local control and resectability rate, but also disease-free and overall survival rate. In a randomized controlled phase I/II clinical trial of ultrasound hyperthermia for advanced head and neck squamous carcinoma, Guoxin Ren et al. found that patients in the ultrasound hyperthermia group had significantly higher efficiency compared with the chemotherapy alone group, and six patients with advanced unresectable head and neck squamous carcinoma regained surgical indications without serious toxic side effects associated with ultrasound hyperthermia [19]. In an ongoing prospective, randomized, multicenter phase II clinical trial of an ultrasound hyperthermia system for the treatment of locally advanced oral squamous carcinoma (registration number: ChiCTR1800014391), a total of 120 patients with oral squamous carcinoma whose clinical stage was consistent with locally advanced resectable (AJCC stage III to IVa) were enrolled in 3 study centers. The trial group was treated with ultrasound tumor hyperthermia combined with TPF regimen for induction chemotherapy, and the control group was treated with TPF regimen alone for induction chemotherapy at 42 ± 1 °C with a heating time of 45 min, with 1 cycle every 21 days for a total of 2 cycles, and surgery within 2 weeks after induction chemotherapy with postoperative supplemental radiotherapy. At present, all enrolled patients have completed the treatment plan and entered the long-term follow-up phase. Preliminary results showed that the recent efficacy of patients in the experimental group was significantly improved, with a recent remission rate of 64.4% in the experimental group and 42.4% in the control group, an improvement of about 22%. The 2-year disease free survival (DFS) of patients in the ultrasound hyperthermia group was significantly prolonged, and only 2 patients developed superficial II degree skin burns, and the systemic toxic side effects of hyperthermia were dominated by bone marrow The systemic side effects of hyperthermia were mainly bone marrow suppression and gastrointestinal reactions, which were not aggravated compared with chemotherapy alone. This indicates that ultrasound hyperthermia has a good promotion prospect in oral squamous carcinoma.

3 Indications and contraindications of ultrasound hyperthermia for oral and maxillofacial head and neck tumors

3.1 Indications

(1) Advanced oral maxillofacial-head and neck malignant tumors (T1-3N1M0, T4aN0-1M0 or T1-4aN2M0) that require preoperative or pre-radiotherapy induction chemotherapy can be combined with local ultrasound hyperthermia therapy to downgrade the clinical stage and improve the surgical cure rate as much as possible.
(2) Salvage treatment of advanced inoperable head and neck malignancies (T1-4cN3M0 or T4b N1-3M0), which can control the primary foci or neck metastases, reduce pain and other symptoms, and improve the quality of life through ultrasound hyperthermia.
(3) There is a palpable mass as the heating target area, with normal surface skin and a depth of no more than 5 cm, and no cavity or bone tissue obscured in the access.

3.2 Contraindications

(1) Skin breakdown on the surface of the tumor in the area to be treated with heat; or severe radiation injury; or extensive postoperative skin scarring; or the presence of titanium plates, implants, or metal crown restorations.
(2) Dull pain response and loss of sensation in the skin of the anticipated therapeutic access.
(3) Have significant organ failure that cannot tolerate treatment.
(4) Tumors containing air cavity organs.
(5) Those with venous emboli in the ultrasound-treated access, or significant calcification in the arterial vessel wall in the access.
(6) Extent of tumor that cannot be clearly visualized by an on-board localization imaging system.
(7) Those with severe coagulation dysfunction, bleeding tendency.
(8) Having severe infection, fever and other complications.
(9) Poor compliance, unable to cooperate with the completion of treatment.

4 Recommended drugs, drug delivery method and heating temperature and time for ultrasound hyperthermia for oral and maxillofacial head and neck tumor patients

4.1 Heating process

4.1.1 Patient preparation

Before treatment, systemic and specialized examinations of important organs of the patient's whole body and other related laboratory tests such as blood routine and blood biochemistry are conducted to exclude contraindications to combined treatment with hyperthermia and chemotherapy. For patients with, for example, low white blood cells, abnormal liver and kidney functions, treatment should be carried out only after symptomatic treatment and restoration of normalcy. The type of pathology must be determined by biopsy before hyperthermia. The tumor volume and scope must be measured with the help of imaging examination before and after the heat therapy in order to judge the efficacy.

4.1.2 Heating process

In hyperthermia, local heating is usually started 30 min after the infusion of chemotherapeutic drugs to achieve the purpose of simultaneous hyperthermia. The expert group recommends ultrasound hyperthermia instrument heating temperature of 42℃ ± 1℃, heating time of 30 ~ 45 min, and output power of 25W. In order to prevent the occurrence of thermal tolerance, the interval between 2 hyperthermia sessions is 48 h, and ultrasound hyperthermia is recommended for 1 cycle for treatment d1, d3, d5, d7, and d9.

4.2 Recommended chemotherapeutic drugs and regimens

The drugs used for ultrasound hyperthermia should be the first-line drugs used clinically for the treatment of oral squamous carcinoma, and the synergistic effect with hyperthermia has been confirmed in basic experiments. Based on this principle, the panel recommends the (docetaxel + cisplatin + 5-Fu) TPF regimen as the first-line regimen for ultrasound hyperthermia, and the second-line drugs can be methotrexate, bleomycin, nedaplatin, etc. Other recommended combination chemotherapy regimens are: cisplatin + 5-Fu (PF regimen), docetaxel + cisplatin (TP regimen). The above regimens can be selected on a case-by-case basis, but the TPF regimen is recommended in preference to neoadjuvant chemotherapy and sequential chemotherapy, and the PF or TP regimen is recommended in preference to combined radiotherapy or targeted therapy [20].

4.3 Precautions during ultrasound hyperthermia

(1) Keep the wound clean and routinely disinfect it before and after treatment.
(2) Local skin scalding blisters during treatment should be treated promptly and treatment should be suspended if necessary.

(3) Regularly review for the first 1 to 2 months after surgery to evaluate treatment effects and adverse reactions.
(4) The scanning range should generally exceed 2 mm beyond the lesion margin.
(5) Attention should be paid to rest and reasonable diet and nutrition during the treatment.
(6) Fever care: for those who have low fever after treatment, no special treatment can be given; if the body temperature is greater than 38℃, heating treatment should be suspended. For those who sweat a lot, attention should be paid to rehydration to prevent accidents such as deficiency.
(7) The heating temperature must be monitored during the heat therapy, and the patient's reaction must be observed to avoid local burns. Since the patient's subjective response such as pain is crucial to the prevention of local burns, local hyperthermia is generally not used for anesthesia.
(8) Ultrasound hyperthermia does not require electromagnetic radiation, so it does not need to be performed in a special shielded room. Health care workers and patients do not need to wear protective clothing, hats, glasses, etc. For the tissues to be protected, it is sufficient to shield them with solid media (e.g., cardboard, film) in their corresponding body surface area [21].

5 Efficacy of ultrasound hyperthermia, evaluation criteria for adverse reactions and treatment of adverse reactions

5.1 Criteria for evaluating the efficacy and adverse reactions of ultrasound hyperthermia

The efficacy evaluation is recommended to refer to the RECIST (V1.1) efficacy evaluation criteria for solid tumors [22], the evaluation criteria for ultrasound hyperthermia-related adverse reactions are recommended to evaluate the severity of skin burns [23], and the evaluation criteria for chemotherapy-related adverse reactions are recommended to evaluate the severity of chemotherapy adverse reactions by CTCAE (V4.0) [24].

5.2 Ultrasound hyperthermia adverse reaction management

The principle of ultrasound hyperthermia-related adverse reactions treatment is that I degree and shallow II degree burns should not be treated, and deep II degree and III degree burns should be immediately stopped from ultrasound hyperthermia treatment and treated according to the principle of skin burn treatment; the principle of chemotherapy-related adverse reactions treatment is the same as conventional chemotherapy [25, 26].

At present, ultrasound hyperthermia has become a hot spot in life science and medical research, and its research results have provided a solid foundation for ultrasound hyperthermia; at the same time, clinical practice has also proved that ultrasound hyperthermia can increase drug efficacy and is safe and reliable, which is worthy of clinical promotion and application. However, there are still many problems that need to be studied in depth. Although it is generally proved that ultrasound hyperthermia can enhance the efficacy of chemotherapy, there is still little evidence from randomized multicenter clinical trials with large samples, and there is also a lack of stratified analysis data, and the influence of gender, age, different stages of tumors, different genetic background and living habits on the efficacy of ultrasound hyperthermia needs to be further clarified. This guideline aims to promote and popularize the diagnosis and treatment standard of ultrasound hyperthermia for oral and maxillofacial tumors head and neck tumors, so as to optimize the treatment of patients with this tumor, with the aim of improving the survival rate and quality of life of patients in the long term. With the emergence of new research results, the expert committee will keep abreast of the times and update this guideline periodically to better meet the people's needs for a healthy life.

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