

## **Cryosurgery with local microwave hyperthermia in oral cavity cancer treatment**

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**Summary:** Complex treatment method employing chemo-radiation therapy (CRT), tumor cryodestruction (CD) followed by local microwave hyperthermia in 24 hours was developed and applied at cancer of mucous membrane of oral cavity and tongue. Treatment results comparative analysis was made for two groups of patients. Control group included 38 patients with cancer of mucous membrane of oral cavity and tongue, whose complex treatment included chemo-radiation therapy (CRT) and tumor cryodestruction (CD). In experimental group of 20 analogous patients, local microwave hyperthermia in 24 hours following CD was added to CRT and CD. Cancer relapse rate in first 12 months of follow-up was - in control group  $31.6\pm 7.54\%$ , in experimental group  $7.70\pm 5.96\%$ . Regional metastases rate for all observation period was  $34.2\pm 7.96\%$  in control group and 0% in experimental group.

**Key words:** cryodestruction, local microwave hyperthermia, antitumor efficiency, cancer of mucous membrane of oral cavity.

### **Introduction:**

Anatomic structure and function of oral cavity mucous membrane determine clinical manifestation of malignant tumors that in the majority of cases have structure of squamous cell cancer.

Due to high rate of primarily advanced malignant tumors of oral cavity and emergence of cancerous tumors forms resistant to chemotherapy the problem of improvement of methods of this localization cancer treatment remains actual.

Principal method of treatment for squamous cell cancer of oral cavity remains surgical treatment, which goal is local tumor and neck lymph nodes removal. Nevertheless combined or extensive operations that are performed in patients with locally advanced cancer of oral cavity lead to severe functional disorders and patient's quality of life deterioration. Above determines the necessity of radio- and chemotherapy application at the first treatment stage. Surgery remains for treatment of small primary tumors that are resistant to chemotherapy or for recurrent tumors. In spite of radical local resection of squamous cell cancer of oral cavity relapse rate makes from 25% to 48% [1,2]. Relapse of oral cavity cancer has tendency to emerge at the primary site, likely from resistant malignant cells in local lymph or from cells on resection margin, and usually it is observed during first 36 months after treatment beginning [3]. One of the most important relapse reasons – is presence of tumor cells in resection margins [4]. Slootweg P and coworkers [5] explored resection margins in 394 patients that underwent surgery and found relapse rate 3.9% in patients with negative and 21.9% in patients with positive results of detectable cancer cells in resection margins.

Therefore the most optimal approach for treatment decision in patients with locally-advanced cancer of oral cavity is complex or combined treatment including radiation therapy, chemotherapy and surgery. Radiation therapy is not an adequate method for primary treatment of late stages of squamous cell oral cavity cancer according to the development of complications due to high risk of necrosis of mucous and bone structures caused by high radiation doses necessary for tumor devitalization [6-7].

Chemotherapy is more frequently used as radiosensitizer in patients with locally-regional relapse or distant metastases and also as neoadjuvant treatment to improve resectability in patients with T4.

For treatment of head and neck malignant tumors cryosurgery also currently applied as independent or integral method in complex treatment [8]. Cryosurgery is a treatment method based on application of biological effects that develop in tissues in response to cooling to ultra-low temperatures. CD secures preservation of anatomic form and structure of affected organs, which has special importance at neoplasma localization in oral cavity [9].

Cryosurgical operations advantages comparing with traditional operations are obvious: performance simplicity, and at the same time high precision, exsanguinity and indolence.

At the same time, cryogenic method possibilities in neoplastic diseases treatment do not guarantee pathological tissue complete destruction [10]. Among the methods of CD effect intensification application of repeated freeze-thawing cycles, prior ischemia creation, combination with ultrasound, with tumor overheating in a form of total and local hyperthermia became a frequent practice.

According to the opinion of Shafranov V.B. and coauthors [10] among the numerous methods of intensification of cryogenic action destructive effect the most effective is preliminary irradiation with microwave field following with instrumental cryodestruction. Microwave hyperthermia is accomplished by special instrument of centimetric wave band of “Parus – 1” and “Yakhta – 3” type. In the published works clear procedures of local microwave hyperthermia application taking into consideration maxillo-facial area and process development stage were not described, also optimal sessions’ number, instrument functioning duration and regimen were not determined.

### **Study materials and methods**

We have provided analysis of complex treatment results with CD application in 58 patients with squamous cell cancer of oral cavity, including 27 patients with tongue cancer and 31 patients with cancer of mucous membrane of oral cavity of different localization. In all cases, the diagnosis was confirmed by tumor histological examination. Neoplasias corresponding to symbol T1 – were in 2, T2 – in 23, T3 –

in 24, and T4 – in 9 patients. Patients' distribution according to tumour localization, patient's age and gender are shown in the Table 1.

. All patients were divided into 2 groups. First (control) group of 38 persons included patients, whose complex treatment included CRT and tumour CD. In the second (experimental) group of 20 analogous patients, to CRT and CD local microwave hyperthermia was added, which was performed 24 hours after CD. Cryogenic action was performed in a form of cryoapplication procedure according to medical procedures developed in the clinic with domestic medical cryogenic instruments "Cryoelectronica" (Ukraine) or "Cryoton-3" (Ukraine). CD as initial stage of complex treatment was applied only in 2 patients; in 29 patients with cancer of mucous membrane of oral cavity and in 27 patients with tongue cancer it was applied as part of complex treatment after CRT after reaching tumour partial regression. Indications for CD conducting in cancer of mucous membrane of oral cavity and tongue cancer were neoplasias with clear margins at superficial and exophytic growth types. CD application is considered as contraindicated in cases of infiltrative neoplasia character, and indistinct lesion margins.

CD did not result in patients' general state deterioration. The treatment usually was conducted under local anesthesia, and was well tolerated even by elderly persons with severe concomitant diseases.

To intensify antitumor effect of cryogenic action tumour microwave field irradiation was applied in 24 hours after CD provided.

Tumour CD with subsequent local microwave hyperthermia was performed in 20 patients, aged from 39 to 78, 9 patients were older than 62 years. Seven patients had tongue cancer, 13 - cancer of mucous membrane of oral cavity. In 18 patients CD with microwave hyperthermia was performed after CRT, on average, in 1.5 months that was optimal time interval for post-radiation tissues reaction remitting. In 2 patients first stage in complex cancer treatment was tumour CD with local microwave hyperthermia. Interval between CD with microwave hyperthermia and subsequent chemo-radiation therapy was within 1 month – the time necessary for mucous membrane epithelization after cryogenic treatment provided.

Local microwave hyperthermia was performed with instrument “Yakhta-3” (Russia). At the beginning of work heating temperature was measured by invasive sensor (copper-constantan thermocouple). Time of hyperthermia action depended on tumor dimensions and its growth form, and was on average 15-20 minutes at average temperature in tumor tissue 42–43°C. Procedure of microwave hyperthermia application was the following. Special antennas for microwave hyperthermia energy supply were introduced into oral cavity directly to the tumour, microwave hyperthermia was accomplished by contact method.

### **Results and discussion**

At follow-up of 38 control group patients after tumor CD in combination with neoadjuvant and adjuvant CRT in the period up to 5 years complete recovery was found in 18 patients (47.4%), including 10 patients (55.5%) with cancer of mucous membrane of oral cavity and 8 patients (40.0%) with tongue cancer.

Good functional and aesthetical results without additional reconstructive interventions were registered. In cases of regional metastases development in neck lymph nodes in 13 patients (34.2%) cellular tissue and lymph nodes excision was performed at the side of lesion. Of this number of patients regional metastases were predominantly diagnosed at tongue cancer in 9 patients (69.2%). During follow-up period in patients after CD regional metastases developed only in 3 patients (23.0%) from 13 patients, all these three patients had tongue cancer. Tumor growth relapses were registered in 20 patients (52.6%) during the periods from 3 to 48 months, from them 12 patients had tongue cancer, and 8 – cancer of mucous membrane of oral cavity. During the first 12 months tongue cancer relapses were revealed in 6 patients (30.0%), relapses of cancer of mucous membrane of oral cavity – in 6 patients (33.3%). During all observation period relapses were diagnosed at II disease stage in 46.6% of cases, at II stage – in 66.7%, at IV stage – in 37.5%.

Follow-up periods for 20 patients after complex treatment with application of neoadjuvant CRT, tumour CD with subsequent local microwave hyperthermia were from 1 year to 2 years. Tumour relapse was determined in one patient

(7.70%) with III stage of cancer of mucous membrane of oral cavity 6 months after CD. During the stated follow-up period regional metastases were not detected (Table 2).

As theoretical basis for such order of tumor CD and local microwave hyperthermia we used the results of our experimental studies [11], in which it was determined that pO<sub>2</sub> level in tumour tissue after CD decreases sharply to zero values. Polarographic studies in 24 and 48 hours after CD confirmed that study tissue is in deep hypoxia conditions, which is caused by vascular stasis. pH reduction also increases sensitivity to hyperthermia. Experiments on animals demonstrated that hyperthermia and its combination with irradiation caused more severe cells death if the cells were in alkali environment [12]. In our research at determination of pH level of tumour tissue homogenate it was registered that in 1 hour after CD reliable differences with control were absent. In 24 hours this index grew up, and in 48 hours it increased reliably from  $6.5 \pm 0.07$  to  $7.0 \pm 0.04$  ( $p < 0.05$ ). These results show that tumor freezing is accompanied with expressed vascular stasis that leads to increase of necrobiotic alterations in tissues and its alkalization. Therefore, in tumor tissue that undergoes CD beneficial conditions for hyperthermia accomplishment develop in 24 hours [11]. Obtained experimental studies data have found confirmation in results of clinical observation over the patients with cancer of mucous membrane of oral cavity and tongue.

In such a way at comparison of the results of complex patients' treatment with application of tumour CD and patients after CD with subsequent microwave hyperthermia relapses rate in the first group 7 times exceeded relapses rate in the second group (52.6% versus 7.70%). Regional metastases rate in the first group of patients was 34.2%, in the second group regional metastases were not detected.

Improvement of indices of relapse-free follow-up period in patients after combined application of low temperatures and microwave hyperthermia is likely to be associated with alteration of immune system reactivity in response to necrosis development and cryonecrosis resorption. Tumor tissue development and its

gradual resorption may influence significantly on alterations of cytotoxic activity of immune system cells [13, 14, 15].

### **Conclusions**

1. In complex treatment choice for patients with cancer of mucous membrane of oral cavity and tongue of II-IV stages it is expedient in 1-1.5 month after conducted CRT to provide tumor CD with subsequent local microwave hyperthermia in 24 hours.
2. Complex treatment application according to the proposed scheme allowed to decrease significantly tumor relapses and regional metastases rates. During the first 12 months of follow-up relapses rate decreased from 31.6 % to 7.7 %. During observation period from 1 to 2 years in study group of patients regional metastases were not detected. In control patients' group regional metastases rate was 34.2%.
3. Combination of two physical factors allowed to increase significantly tumor destruction degree, to reduce its recurrence rate and thereby to increase treatment efficacy.

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**Table N 1. Patients' distribution according to tumour localization, patient's age and gender.**

| Localization                   | Gender | Patient's age |       |       |       |       |      | Total |
|--------------------------------|--------|---------------|-------|-------|-------|-------|------|-------|
|                                |        | 30-40         | 41-50 | 51-60 | 61-70 | 71-80 | > 80 |       |
| Mucous membrane of oral cavity | M      | 1             | 5     | 6     | 10    | 5     | -    | 27    |
|                                | F      | -             | -     | 2     | -     | 1     | 1    | 4     |
| Tongue                         | M      | 2             | 2     | 12    | 6     | 2     | -    | 24    |
|                                | F      | 1             | 1     | 1     | -     | -     | -    | 3     |
| Total                          |        | 4             | 8     | 21    | 16    | 8     | 1    | 58    |

**Table N 2. Relapses and regional metastases rate in study patients' groups.**

| Complex treatment                     | Tumor localization                       | Number of patients | Relapses            |                  | Regional metastases |
|---------------------------------------|--|--------------------|---------------------|------------------|---------------------|
|                                       |  |                    | total               | During 12 months |                     |
| CRT+CD                                | Tongue cancer                            | 20                 | 12<br>(60.0±10.95%) | 6 (30.0 %)       | 9 (45.0 %)          |
|                                       | Cancer of mucous membrane of oral cavity | 18                 | 8<br>(44.4±11.7%)   | 6 (33.3%)        | 4 (22.2 %)          |
| CRT+CD<br>+<br>Microwave hyperthermia | Tongue cancer                            | 7                  | -                   | -                | -                   |
|                                       | Cancer of mucous membrane of oral cavity | 13                 | 1<br>(7.70±7.39%)   | -                | -                   |

CRT – Chemo-radiation therapy

CD – Tumor cryodestruction