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Interstitial brachytherapy of oral squamous cell carcinoma with ultrasound-guided iodine-125 radioactive seed implantation

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Abstract. – OBJECTIVE: In this study, we investigated the clinical effect of interstitial brachytherapy on oral squamous cell carcinoma (OSCC) with ultrasound or CT-guided ^{125}I radioactive seed implantation.

PATIENTS AND METHODS: 116 patients with advanced oral squamous cell carcinoma, who received initial treatment or retreatment, were enrolled. Therein, 35 patients in the control group were treated with external radiation, systemic chemotherapy or conservative treatment, 41 patients in the ultrasound group were treated with ultrasound-guided^{125}I radioactive seed interstitial implantation brachytherapy, and 40 patients in the CT group were treated with CT-guided ^{125}I radioactive seed interstitial implantation. The median follow-up time was 15.0 months. The clinical outcomes were compared.

RESULTS: At the time of one month after treatment, the tumor diameters of the ultrasound group and the CT group were significantly decreased (p<0.05), which were less than the control group (p<0.05), and there was no difference in comparison between the ultrasound group and the CT group (p>0.05). At the time of one month after treatment, the effective rates were significantly higher in the ultrasound group and the CT group than the control group (p<0.001), and there was no difference in comparison between the ultrasound group and the CT group. And there was no difference in comparison of complication between these two groups (p>0.05). At the time of one month after treatment, the VAS scores of pain were significantly lower in the ultrasound group and the CT group than the control group (p<0.05). There were no differences in comparisons of T lymphocyte subset percentages before and after treatment (p>0.05), and T lymphocyte subset percentages in the control group were significantly decreased (p<0.05). The progression-free survivals, median survival times, and survival rates were significantly higher in the ultrasound group and the CT group than those in the control group (p<0.05), and there were no differences in comparisons between the ultrasound group and the CT group (p>0.05).

CONCLUSIONS: Both ultrasound and CT-guided iodine-125 radioactive seed interstitial implantation brachytherapy in the treatment of OSCC can achieve better short-term and long-term clinical effects.

Key Words:
Ultrasound-guided, ^{125}I radioactive seed, Interstitial implantation, Oral squamous cell carcinoma.

Introduction

Statistically, the incidence rate of malignant tumor of the oral cavity accounts for approximately 4.0-8.5% of the general tumor, and the 5-year survival rate can be increased to 30-70% by using comprehensive treatment methods, such as surgery, radiotherapy, and chemotherapy[1]. Local recurrence and metastasis are the main causes leading to death[2]. About 40-60% of patients are in the middle and late stage at the time of initial diagnosis, which means that surgical resection is less likely; moreover, for patients with postoperative recurrence, the probability of re-operation or radiotherapy and chemotherapy is greatly reduced[3]. It has been confirmed that the application of ^{125}I radioactive seed interstitial implantation brachytherapy in the treatment of prostate cancer, liver cancer, pancreatic cancer, and lung cancer has better safety and effectiveness[4-6]. The tumor killing efficiency is enhanced, and the radiation damage of the surrounding normal tissue is decreased when the local seed concentration is significantly increased. With the aid of CT or ultrasound imaging, this treatment technique significantly decreases the total radiation dose, shortens the course of radiation, and reduces the complications of radiotherapy as well as the pain of patients through the accurate positioning and measurement, which is of great significance to

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improve the survival outcome[7,8]. This study summarizes the clinical effect of ^{125}I radiotherapy on patients with advanced oral squamous cell carcinoma which provides reference basis for the rational choice of treatment strategy.

Patients and Methods

Patients

A total of 116 patients with advanced OSCC, who received initial treatment or retreatment in our hospital from March 2013 to March 2016, were continuously selected. *Inclusion criteria:* a) The diagnosis was confirmed by pathology, and KPS was more than or equal to 80 points; b) The seed implantation was successful; c) The treatment compliance was good, the clinical data was perfect, and the informed consent of patient was obtained. Informed consent was confirmed according to the Ethical Committee of Henan Provincial People's Hospital. *Exclusion criteria:* The patients, who were complicated with a primary malignant tumor in other parts of the body and metastatic tumor of the neck, with no distant metastasis to other organs, were excluded. The patients were divided into three groups in accordance with the treatment plans. Therein, 35 patients in the control group were treated with external radiation, systemic chemotherapy or conservative treatment, 41 patients in the ultrasound group were treated with ultrasound-guided iodine-125 radioactive seed interstitial implantation brachytherapy, and 40 patients in the CT group were treated with CT-guided iodine-125 radioactive seed interstitial implantation. Baseline data among the three groups were comparable (Table I).

Research Method

The patients in the control group were treated with conventional radiotherapy and chemotherapy or conservative treatment. DF chemotherapy regimen was the main method, namely oxaliplatin 150 mg + tegafur 7 g. The patients received continuous 6-7 courses of treatment, each interval of 21 days. The three-step analgesic ladder therapy recommended by the WHO was used to stop the pain.

^{125}Iradioactive seeds, TRH-I type radioactive seed implantation guns, protective equipment and seed loading platforms were provided by HTA Co., Ltd. of Beijing. The high purity titanium tube wrapped silver structures containingradioactive^{125}I, with the length of 4.5±0.3 mm, and the external diameter of 0.8±0.03 mm. The energy of ^{125}I was 22 keV, the half-life was 59.43 days, the activity was 0.7-0.8mCi, and the prescription dose was 120-160Gy. 18G radioactive seed implant needles were provided by Riyi Company (Tokyo, Japan), and the computer-assisted three-dimensional treatment planning system (TPS) was provided by TPS treatment planning center of Beijing University of Aeronautics and Astronautics. The ultrasound was Philips iU22 type (Bothell, WA, USA), and CT was GE 64-slice spiral computed tomography (Stamford, CT, USA). Patients in the ultrasound group and the CT group were examined one week before the operation to determine the lesion size, location and the surrounding tissue relationship of the target area. The obtained image information was imported into Treatment Planning System (TPS), and then the target area was delineated using image layer by layer. The three-dimensional reconstruction, radiation dose, equal dose plane of seed does field, and other data were analyzed, and the mutually parallel seed implantation planes were selected for simulating seed implantation. According to the principle of radiotherapy, 90% target area volume should receive 90% prescription dose, and the peripheral organ receiving dose remained in the range of normal tolerance. Then, the direction and position of implant needle, as well as the number of seeds, were adjusted. The patient was kept in the supine position, and the shoulder was blocked up, with the

Table I. Comparisons of three groups of baseline data.

Groups	Control Group (n=35)	Ultrasound group (n=41)	CT Group (n=40)	F/χ^2	*p*
Male/female	19/16	22/19	20/20	0.167	0.920
Age (y)	57.6±12.3	56.9±13.4	58.2±13.9	0.185	0.867
Initial treatment/retreatment	9/26	12/29	10/30	0.214	0.898
Tumor location				0.564	0.997
Tongue	11	13	12		
Buccal mucosa	12	15	13		
Mouth floor	3	5	5		
Parotid gland	9	9	10		

Table II. Comparisons of tumor diameters before and after treatment (cm).

Groups	Control group	Ultrasound group	CT group	F	*p*
Before treatment	3.9±1.6	4.1±1.8	4.2±1.7	0.196	0.823
One month after treatment	4.2±1.8	2.6±1.3	2.7±1.5	6.532	0.006
t-value	3.659	4.587	4.432		
p-value	0.032	0.024	0.026		

general anesthesia. Based on the preoperative TPS design, the needle insertion point and angle of the implant needle were determined under the guidance of the ultrasound or CT, guiding the implant needle to avoid blood vessels and other important tissues. The reference point was selected at about 0.5 cm around the target area. When the implant needle reached the margin of the tumor, the seeds were implanted. The needle gradually retreated with the equidistance of 1.0 cm and released seeds, until the end of a row, the seed implant needle was retracted out and, then, pressure was applied to stop the bleeding. The seed distribution was square or triangular, with equal distance, and then the repeat operation was performed for the next row until the end of a layer. Finally, whether the target area was covered and whether the distribution was uniform should be checked; then, the design diagram was printed. After the operation, the implantation area was covered and enswathed with aseptic dressing for preventing the capillary hemorrhage and infection of the implanted channel.

The vital signs were closely monitored, and the blood routine, liver and kidney functions, blood coagulation indexes and others were examined. The implantation area was sterilized, and the dressing was replaced. The conventional anti-infection therapy was performed for three days.

Observation Index and Detection Method

The tumor diameters, therapeutic effects and complications, VAS scores of pain, percentages of T lymphocyte subset in peripheral blood, follow-ups of progression-free survivals, median survival times, and survival rates of the target areas before and after treatment among three groups were compared. The regular follow-up was performed at the time point of one month after operation as well as three months for an interval, and the tumor diameter was evaluated by ultrasound and CT, respectively. The record and statistical analysis were completed by the third-party researchers. According to the short-term Response Evaluation Criteria in Solid Tumors (RECIST), the therapeutic effects were divided into complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD). Therein, CR was defined as the complete disappearance of the lesion lasting for at least one month. PR referred to the situation where the size of the lesion decreased by more than 50% and then remained unchanged for at least one month. SD was defined as the situation where the size of the tumor decreased by less than 50% or increased by less than 25%. PD referred to the situation where the size of the tumor increased by more than 25%. VAS scores were divided into 0-10 grades using numerical method, and the higher the score, the more severe the pain would be. T lymphocyte subsets, including CD4+, CD8+ cells, and NK cells were detected by flow cytometry. Flow cytometer was performed with a FACSCaliber (BD Biosciences, Franklin Lakes, NJ, USA). The median follow-up time was 15.0 months.

Statistical Analysis

SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Measurement data were expressed as mean ± SD. The single factor ANOVA was adopted in comparisons among the groups. The LSD test method was adopted in testing pairwise comparison, and paired *t*-test was adopted for the comparison in each group. The count data was expressed by case or percentage, and chi-square test was used in comparison among the groups. Wilcoxon was used for the rank data. Kaplan-Meier model and log-rank χ^2-test were adopted for progression-free survival and median survival time. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of Tumor Diameters Before and After Treatment

One month after treatment, the tumor diameters of the ultrasound group and the CT group were significantly decreased ($p<0.05$). They were

Table III. Comparisons of therapeutic effects [case (%)].

Groups	CR	PR	SD	PD	Total effective rate
Control group (n=35)	0	10	12	13	10 (28.6)
Ultrasound group (n=41)	8	24	5	4	32 (78.0)
CT group (n=40)	8	25	4	3	33 (82.5)

Table IV. Comparisons of VAS scores of pain and lymphocyte percentages.

Groups		Control group	Ultrasound group	CT group	*F*	*p*
VAS score	Before treatment	2.5±1.2	2.6±1.3	2.4±1.4	0.096	0.957
	One month after treatment	3.4±1.5	2.0±1.2	1.9±1.3	5.562	0.014
CD4+ (%)	Before treatment	37.6±12.3	36.9±12.5	37.5±12.7	0.132	0.832
	One month after treatment	30.9±11.2	37.2±12.6	37.3±12.4	5.429	0.013
CD8+	Before treatment	32.4±13.6	33.5±13.3	31.9±13.5	0.128	0.865
	One month after treatment	26.5±12.1	34.2±12.9	33.3±12.6	5.321	0.016
NK cell	Before treatment	17.8±9.5	16.9±9.3	17.4±9.5	0.212	0.787
	One month after treatment	11.7±6.3	14.5±8.7	15.6±8.6	5.029	0.021

fewer than the control group ($p<0.05$), and there was no difference between the ultrasound group and the CT group ($p>0.05$) (Table II).

Therapeutic Effects and Complications

One month after treatment, the effective rates were significantly higher in the ultrasound group and the CT group than the control group ($\chi^2=28.734$, $p<0.001$), and there was no difference between the ultrasound group and the CT group ($\chi^2=0.253$, $p=0.615$, $Z=-0.351$, $p=0.725$) (Table III). There were 4 cases (9.8%) of patients with complications in the ultrasound group, dental ulcer in 1 case, fever in 1 case, and seed migration or abscission in 2 cases.There were 4 cases (10.0%) of patients with complications in the CT group, dental ulcer in 1 case, infection in 1 case, wound delay healing in 1 case, and seed migration or abscission in 1 case. There was no difference between the two groups ($\chi^2=0.000$, $p=1.000$).

VAS scores of pain and T lymphocyte subgroup percentages

At the time of one month after treatment, the VAS scores of pain were significantly lower in the ultrasound group and the CT group than the control group ($p<0.05$). There were no differences in T lymphocyte subset percentages before and after treatment ($p>0.05$), and T lymphocyte subset percentages in the control group were significantly decreased ($p<0.05$) (Table IV).

Follow-ups of Progression-free Survivals, Median Survival Times and Survival Rates

The progression-free survivals, median survival times, and survival rates were significantly higher in the ultrasound group and the CT group than the control group ($p<0.05$), and there were no differences between the ultrasound group and the CT group ($p>0.05$) (Table V).

Discussion

The previous study[9] has confirmed that the penetration distance of ^{125}I is 1.7 cm, with small damages to the surrounding tissues, of which the effective killing effect on the tumor can reach more than five half-lives. Moreover, seeds with the gradual accumulation of radiation doses en-

Table V. Comparisons of follow-ups of progression-free survivals, median survival times, and survival rates.

Groups	Control group (n=35)	Ultrasound Group (n=41)	CT group (n=40)	χ^2	*p*
Progression-free survival (month)	3.5	6.9	7.1	6.532	0.000
Median survival time (month)	10.2	17.8	17.5	7.212	0.000
Survival rate [case (%)]	10 (28.6)	30 (73.2)	31 (77.5)	22.643	0.000

hance the effect of killing tumors. Preoperative accurate treatment planning, accurate implantation of seeds during operation, and the timely verification of the quality are very important[10]. By using TBS, the dose of the target area is highly conformal to the tumor area. At the same time, the dose of important tissues around the target area is also in the safe range. Since the tissue structure of the oral and maxillofacial region is more complex and the arrangement is more compact, the guidance of imaging is required. Compared to CT, ultrasound has some advantages as follows[11,12]: a) The tumor size, shape, and its relationship with the surrounding tissues can be clearly displayed, and the seed needle is monitored in real time. Thus, the insertion point and the direction of seed implant needle can be adjusted at any time; b) The blood flow of tumor target area and the surrounding tissues are clearly displayed; this can prevent the insertion of seed implant needle into the blood vessels avoiding the bleeding or the formation of emboli; c) It has the characteristics of non-invasion, repetitive operation, and no radiation. This work concluded that, one month after treatment of the ultrasound group and the CT group, the tumor diameters were significantly decreased, the effective rates were enhanced, the VAS scores of pain were decreased. The progression-free survivals, median survival times, and survival rates were increased, and there were no differences in the percentages of T lymphocyte subsets before and after treatment. Both ultrasound and CT-guided ^{125}I radioactive seed interstitial implantation brachytherapy in the treatment of oral squamous cell carcinoma can achieve better short-term and long-term clinical effects. Some study[13] also performs the analysis of the treatment time, postoperative hospital stay, the total seed dose and other aspects, which has obtained basically consistent conclusions. Under the guidance of ultrasound, by using a needle insertion point with multiple seed implantation method, the seed implant needle was gradually retreated with the equal distance, so as to place the seeds into the target area, and postoperative quality monitoring basically met the standard. The degree of pain affected the postoperative rehabilitation effect. After the implantation of ^{125}I seeds, the tumor volume is significantly reduced, and the compression of tumor to nerve tissue is relieved. Moreover, the release of local pain inflammatory mediators, such as bradykinin, 5-HT, prostaglandin, and others, is reduced[14]. The conducting functional electrophysiological blocking of tumor peripheral nerve ending or myelin degeneration blocks the conduction of pain. The formation of microthrombus in tumor or cancer adjacent blood vessels leads to the decrease of the permeability of the pain factor; the spatial structure of membrane protein is changed by seed irradiation which reduces or loses the activity of ion channel of the cell membrane, thereby blocking the conduction of nerve impulse[15]. Local swelling and pain may be the inflammatory response caused by the stimulation of implant needle to local tissues rather than the acute radiation injury[16]. A distinct complication of systemic chemotherapy is the suppression of immune function of the body. T lymphocyte-mediated cellular immunity plays an important role in killing tumors. ^{125}I seed implantation keeps a physical effect in the local area of tumor, showing less interference with systemic or local immune function[17]. Moreover, since ultrasound or CT-guided ^{125}I seed implantation has a high precision, the occurrence of seed migration or abscission is less.

Conclusions

This study provides an important reference basis for the rational choice of interstitial brachytherapy of oral squamous cell carcinoma with ultrasound or CT-guided ^{125}I radioactive seed implantation. The negative results of these two methods may be related to the small sample size, short follow-up time, and clinical stages of enrolled disease.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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