Int J Clin Exp Med 2019;12(9):11452-11459
www.ijcem.com /ISSN:1940-5901/IJCEM0096277

*Original Article*

# Effects of radioactive iodine-125 seed implantation on therapeutic efficacy, serum VEGF, CEA levels, and prognosis of patients with ocular malignant tumors

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Received April 29, 2019; Accepted July 11, 2019; Epub September 15, 2019; Published September 30, 2019

**Abstract:** Objective: The aim of the current study was to investigate the effects of radioactive iodine-125 seed implantation on therapeutic efficacy, serum vascular endothelial growth factor (VEGF), carcinoembryonic antigen (CEA) levels, and prognosis of patients with ocular malignant tumors. Methods: A total of 86 patients with ocular malignant tumors were randomly allocated into the adjuvant chemotherapy group or iodine-125 seed implantation group, based on a random number table, with 43 patients in each group. The chemotherapy group underwent ocular tumor resections and routine postoperative adjuvant chemotherapy, while the iodine-125 group was treated with tumor resections and intraoperative iodine-125 seed implantation. At 3 months after surgery, after the chemotherapy group had received 2 cycles of chemotherapy, total effective rates were accessed in both groups. Serum CEA levels, before and after treatment, were detected by automatic electrochemiluminescence. Serum VEGF levels were also measured, before and after treatment, in both groups via ELISA. Correlation levels between CEA and VEGF were analyzed. Incidence rates of side effects, during treatment, were recorded and compared between the two groups. One-year progression-free survival and 3-year survival rates of the two groups were compared via regular follow-ups. Results: The total effective rate of the iodine-125 group was higher than that of chemotherapy group ($P<0.05$). In addition, expression levels of serum CEA and VEFG in the two groups, after treatment, were lower than those before treatment (all $P<0.05$). Decreases in the iodine-125 group were more significant than those in the chemotherapy group (both $P<0.05$). Serum CEA levels and VEGF levels were positively correlated. Incidence of side effects in the iodine-125 group was significantly lower than that in the chemotherapy group ($P<0.05$). Furthermore, 1-year progression-free survival and 3-year survival rates in the iodine-125 group were higher than those in the chemotherapy group. Differences were statistically significant (both $P<0.05$). Conclusion: Radioactive iodine-125 seed implantation in patients with ocular malignant tumors can effectively improve therapeutic efficacy, reduce serum levels of tumor markers CEA and VEGF, and improve 1-year progression-free survival and 3-year survival rates. This method shows a high level of safety. Thus, it is highly recommended for clinical practice.

**Keywords:** Ocular malignant tumors, radioactive iodine-125, CEA, VEGF

## Introduction

Malignant tumors are a major threat to human life, including ocular malignant tumors [1]. Malignant tumors of the eye include malignant melanomas, squamous cell carcinoma, orbital basal cell carcinoma, and conjunctival squamous cell carcinoma. These not only impair eye function but also may spread to the brain, as well as the whole body. Metastasis can threaten patient life while blinding the eyes [2, 3]. A combination of surgery and chemoradiotherapy has been the main treatment for ocular malignancies. Results are difficult to achieve with surgery alone due to the relatively complex structure of the eye [4, 5]. However, destructive procedures, such as eyeball removal or orbitotomy procedures, may seriously damage the eyeball and visual function. In addition, large-area radiotherapy in the eye can cause damage to the surrounding tissues, including radiation cataracts and radiation optic neuropathy [6-8]. Therefore, for patients with ocular malignant tumors, it is of great significance to find a treatment method that can accurately control lesions, while avoiding damage to major eye tissues.

Radioactive iodine-125 seed implantation is a novel treatment method for malignant tumors.

The therapeutic rationale includes using low dosage γ rays. These directly break DNA strands and decompose water molecules to free radicals in the body [9]. Only cells in the mitosis or DNA synthesis phase are sensitive to γ rays. The surrounding normal cells are not [10]. The American Brachytherapy Society has reported that iodine-125 seed implantation is comparable to traditional eyeball removal in patients with choroidal melanoma. However, the former preserves some or all of the patient's vision [11]. At present, iodine-125 seed implantation remains a new treatment method. Few studies have focused on its use in patients with ocular malignant tumors. The current study conducted a randomized controlled trial, investigating the effects of radioactive iodine-125 seed implantation on therapeutic efficacy, serum levels of tumor markers, and prognosis of patients with ocular malignant tumors.

## Materials and methods

### *Patients*

A total of 86 patients with ocular malignant tumors, admitted to West China Hospital of Sichuan University, from June 2014 to January 2016, were randomly allocated into the adjuvant chemotherapy group or iodine-125 seeds implantation group, based on a random number table, with 43 patients in each group. The chemotherapy group underwent ocular tumor resections and routine postoperative adjuvant chemotherapy, while the iodine-125 group was treated with tumor resections and intraoperative iodine-125 seed implantation. All patients agreed to participate in the study and provided informed consent. The patients cooperated with the study and completed the relevant medical treatment. The protocol of this study was approved by the Ethics Committee of West China Hospital of Sichuan University.

### *Inclusion and exclusion criteria*

Inclusion criteria: Patients with ocular malignant tumors, diagnosed by pathological biopsies (striated muscle tumor, monocular retinoblastoma, lacrimal gland tumor, and melanoma).

Exclusion criteria: Patients with severe diseases, such as liver or kidney failure; Patients with severe immune disease; Patients with abnormal coagulation function; Patients with surgical contraindications; Patients that did not cooperate during treatment; Patients with cognitive or mental disorders.

### *Treatment*

All patients underwent tumor resection surgeries, in which the lesions were radically removed. Patients in the iodine-125 group received intraoperative iodine-125 seed implantation. Doses of iodine-125 seeds were determined based on the size and volume of the tumors, as well as the degree of invasion of surrounding tissue. The doses were between 10 and 30 mci. The implantation procedure was guided by a Philips Brilliance 16-row spiral CT. The therapy planning system was purchased from Zhuhai Hokai Co. Ltd., China. The 18G seeds implantation needle (length 4.50 mm, diameter 0.80 mm, cylindrical titanium alloy structure), implantation gun, and radioactive iodine-125 seeds (effective range 17 mm, seed activity 0.53~0.81 mCi, and half-life 59.56 days) were purchased from Beijing Zhibo Co. Ltd., China. At the time of treatment, iodine-125 seeds were taken out with the implantation needle. The seeds were then implanted, according to the wound size, at 1 cm intervals. After implantation, the distribution of iodine-125 seeds was evaluated by CT scans in the implanted area. When it was confirmed that the target therapeutic dosage was reached and no seed displacement had occurred, treatment was complete. Waste materials generated during the operation were processed according to safety standards for disposal of radioactive waste. The chemotherapy group received adjuvant chemotherapy 3 weeks after surgery, based on specific conditions of the patients. The regimen included CAP and AVF. Therapeutic efficacy was evaluated after 2 cycles of chemotherapy, spaced 4 weeks apart.

### *Observational indicators*

At 3 months after surgery, all patients underwent MRI or CT scans, evaluating tumor size changes. Therapeutic efficacy was evaluated and stratified as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD), according to Response Evaluation Criteria in Solid Tumors. Total effective rate = (CR+PR)/total*100% [12]. Serum CEA levels of the two groups, before (one day

**Table 1.** Comparison of general conditions

| Group | Iodine-125 group (n=43) | Chemotherapy group (n=43) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Sex | | | 0.057 | 0.829 |
| Male | 23 (53.49) | 24 (55.81) | | |
| Female | 20 (46.51) | 19 (44.19) | | |
| Age (year) | | | 0.047 | 0.828 |
| ≤52 | 24 (55.81) | 25 (58.14) | | |
| >52 | 19 (44.19) | 18 (41.86) | | |
| BMI ($kg/m^2$) | | | 0.047 | 0.829 |
| ≤22 | 21 (48.84) | 20 (46.51) | | |
| >22 | 22 (51.16) | 23 (53.49) | | |
| Tumor type | | | 0.273 | 0.965 |
| Rhabdomyosarcoma | 10 (23.26) | 11 (25.58) | | |
| Unilateral retinoblastoma | 12 (27.91) | 10 (23.26) | | |
| Lacrimal gland tumors | 11 (25.58) | 12 (27.91) | | |
| Melanoma | 10 (23.26) | 10 (23.26) | | |
| Liver function | | | | |
| Total Protein (g/L) | 72.45±2.23 | 72.15±2.43 | 0.597 | 0.553 |
| Alanine transaminase (μmol/L) | 28.56±4.78 | 27.91±4.85 | 0.627 | 0.532 |
| Total bilirubin (μmol/L) | 11.32±2.01 | 11.27±2.06 | 0.114 | 0.910 |
| Renal function | | | | |
| Serum creatinine (μmol/L) | 67.45±4.23 | 68.12±4.35 | 0.724 | 0.471 |
| Blood urea nitrogen (μmol/L) | 5.17±0.45 | 5.18±0.33 | 0.118 | 0.907 |
| Serum uric acid (μmol/L) | 294.56±10.46 | 292.75±11.49 | 0.764 | 0.447 |

before surgery) and after treatment, were detected by automatic electrochemiluminescence. ELISA was used to measure serum vascular endothelial growth factor (VEGF) levels before and after treatment. Correlation levels between CEA and VEGF were also analyzed. Incidence rates of side effects, during treatment, were recorded and compared between the two groups. Major side effects included nausea and vomiting, leukopenia ($<3.5*10^9/L$), and thrombocytopenia ($<100*10^9/L$). One-year progression-free survival and 3-year survival rates of the two groups were compared via regular follow-ups.

*Statistical analysis*

Present data were analyzed with SPSS18.0 (Asia Analytics Formerly SPSS China) statistical package. Quantitative values are expressed as mean ± sd. Differences between the groups were evaluated using independent t-tests. Differences before and after surgery in each group were evaluated by paired t-tests. Enumeration data were compared by $\chi^2$ tests. Pearson's correlation analysis was performed for serum CEA and VEGF levels. Kaplan-Meier survival curves were drawn. Two curves were compared using log-rank tests. $P<0.05$ indicates statistical significance.

## Results

*Comparison of general conditions*

There were no significant differences in gender, age, BMI, tumor types, and major organ function between the two groups (all $P>0.05$). General conditions of the two groups were, therefore, comparable. See **Table 1**.

*Comparison of total effective rates*

The total effective rate was 88.37% in the iodine-125 group, significantly higher than the 69.77% rate in the chemotherapy group. Differences were statistically significant ($P<0.05$). See **Table 2**.

*Comparison of serum CEA and VEGF*

Serum CEA and VEFG levels, before treatment, in the iodine-125 group were 14.15±4.31

**Table 2.** Comparison of therapeutic efficacy (n, %)

| Group | Iodine-125 group (n=43) | Chemotherapy group (n=43) | $t/\chi^2$ | P |
|---|---|---|---|---|
| CR | 24 (55.81) | 16 (37.21) | | |
| PR | 14 (32.56) | 14 (32.56) | | |
| SD | 4 (9.30) | 7 (16.28) | | |
| PD | 1 (2.33) | 6 (13.95) | | |
| Total effective rate | 38 (88.37) | 30 (69.77) | 4.497 | 0.034 |

Note: CR: complete remission; PR: partial remission; SD: stable disease; PD: Progressive disease.

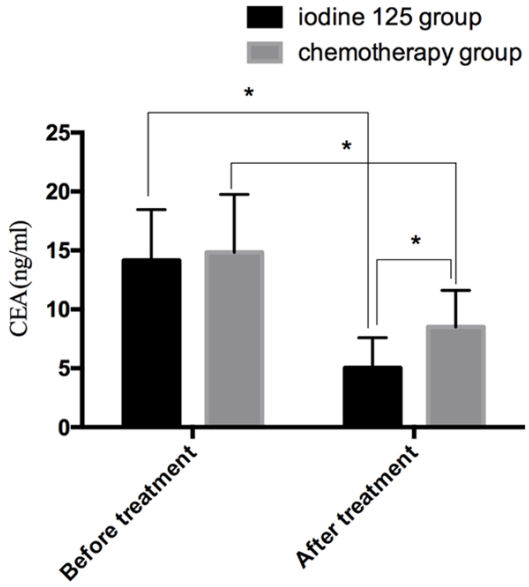


**Figure 1.** Comparison of serum CEA before and after treatment. *P<0.05; CEA: Carcino-embryonic antigen.

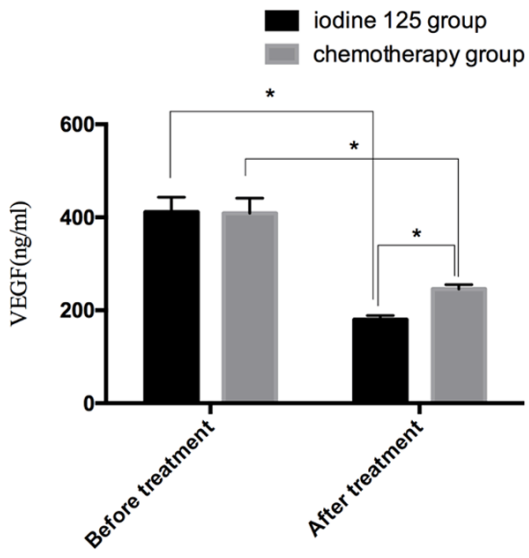


**Figure 2.** Comparison of serum VEGF before and after treatment. *P<0.05; VEGF: Vascular endothelial growth factor.

ng/mL and 411.39±31.58 ng/L, respectively. After treatment, the values were 5.03±2.57 ng/mL and 179.63±9.26 ng/L, respectively. In the chemotherapy group, serum CEA and VEFG levels, before treatment, were 14.84±4.91 ng/mL and 408.76±32.48 ng/L, respectively. After treatment, the values were 8.51±3.11 ng/mL and 245.76±9.42 ng/L, respectively. After treatment, serum CEA and VEFG levels in both groups were significantly lower than those before treatment (all P<0.05). However, patients in the iodine-125 group showed more significant decreases than patients in the chemotherapy group (both P<0.05). See **Figures 1** and **2**.

*Pearson's correlation analysis of serum CEA and VEGF levels*

There was a positive correlation between serum levels of CEA and VEGF (r=0.641, P<0.05). See **Figure 3**.

*Comparison of incidence of major side effects*

In the iodine-125 group, patients with nausea and vomiting, thrombocytopenia, and leukopenia were 2, 1, and 1, respectively. Incidence of side effects was 9.30%. In the chemotherapy group, patients that developed nausea and vomiting, thrombocytopenia, and leukopenia were 6, 6, and 4, respectively. Incidence of side effects was 37.21%, significantly higher than that in the iodine-125 group. Differences were statistically significant (P<0.05), as shown in **Table 3**.

*Comparison of 1-year progression-free survival and 3-year survival rates*

One-year progression-free survival and 3-year survival rates of patients in the iodine-125 group were significantly higher than those in the chemotherapy group (both P<0.05). See **Table 4** and **Figure 4**.

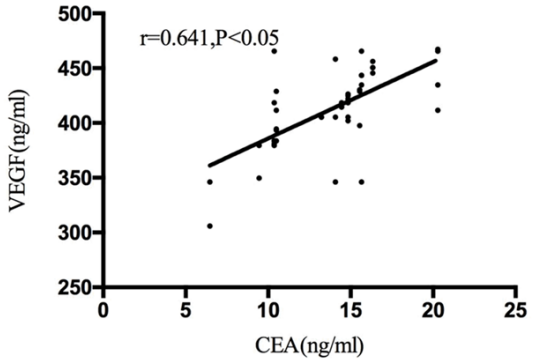


**Figure 3.** Pearson's correlation analysis of serum CEA and VEGF. CEA: Carcino-embryonic antigen; VEGF: Vascular endothelial growth factor.

## Discussion

One of the most important sensory organs of the human body, the eye can help people obtain visual information from the complex environment. Once a tumor appears in the human eye, it will seriously affect quality of life, even threaten lives [13, 14]. Surgery is currently the predominant method for treatment of ocular malignant tumors. However, concurrent chemotherapy, radiotherapy, or immunotherapy have certain effects on ocular malignant tumors [15]. Most patients are at a late stage when diagnosed. As a result, most patients need more destructive treatments, such as eyeball removal, chemotherapy, and large-area radiotherapy procedures. These not only affect the patient's appearance, but also cause side effects, affecting visual function. Sometimes, serious complications may occur and threaten patient lives [16, 17]. Radioactive iodine-125 seed implantation is a close-range radiation therapy with a very short radiation radius. This makes radioprotection relatively easy. In addition, iodine-125 implantation is easy to operate and provides significant therapeutic efficacy and high safety. Thus far, it has been used for cancer treatment in many clinical centers [18]. However, there are few reports concerning radioactive iodine-125 implantation for treatment of ocular malignancies.

The current study found that therapeutic effects in the iodine-125 group were significantly higher than those in the chemotherapy group, suggesting that radioactive iodine-125 seed implantation is more effective for ocular malignant tumors than conventional postoperative chemotherapy. Previous studies have explored the effects of iodine-125 seed implantation in lung cancer. They also indicated that iodine-125 was more effective than conventional radiotherapy and chemotherapy, confirming present results [19].

Evaluation of serum tumor markers is an important indicator concerning therapeutic effects of tumors. CEA is a non-organ specific tumor antigen produced by tumor tissues, usually highly expressed in the serum of tumor patients [20]. VEGF is a homo-dimeric glycoprotein that stimulates biological processes, such as migration and proliferation of vascular endothelial cells. It has been closely related to angiogenesis and tumor metastasis [21]. Therefore, the current study compared serum CEA and VEGF, before and after treatment, in both groups. Results showed that expression of serum CEA and VEFG in the two groups was significantly lower than that before treatment. However, the decline in the iodine-125 group was more pronounced than that in the chemotherapy group. This suggests that, compared with conventional chemotherapy, iodine-125 implantation is more effective in reducing serum levels of CEA and VEGF in patients with ocular malignant tumors. Previous studies have also demonstrated that iodine-125 seed implantation can lower expression levels of serum tumor markers in cancer patients [22]. Current results found that expression between CEA and VEGF was positively correlated. This may be because both CEA and VEGF may change with the occurrence and development of tumors. However, whether there is a specific regulatory relationship between the two markers requires further research. In other studies, researchers have explored the effects of iodine-125 seed implantation on serum levels of tumor markers, such as VEGF, in lung cancer patients. Results were similar to present results [23].

Subsequently, the current study compared incidence rates of side effects of the two groups, during treatment, aiming to investigate safety levels of iodine-125 seed implantation. Results showed that incidence rates of side effects in the iodine-125 group were significantly lower than those in the chemotherapy group. This suggests that iodine-125 has higher safety and less adverse effects than conventional chemotherapy. A previous study, in which iodine-125

**Table 3.** Comparison of side effects (n, %)

| Group | Iodine-125 group (n=43) | Chemotherapy group (n=43) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Nausea and vomiting | 2 (4.65) | 6 (13.95) | | |
| Thrombocytopenia | 1 (2.33) | 6 (13.95) | | |
| Leukopenia | 1 (2.33) | 4 (9.30) | | |
| Incidence of side effects | 4 (9.30) | 16 (37.21) | 9.382 | 0.002 |

**Table 4.** Comparison of 1-year progression-free survival and 3-year survival rates (n, %)

| Group | Iodine-125 group (n=43) | Chemotherapy group (n=43) | $t/\chi^2$ | P |
|---|---|---|---|---|
| 1-year progression-free survival | 31 (72.09) | 19 (44.19) | 6.880 | 0.009 |
| 3-year survival rate | 37 (86.05) | 25 (58.14) | 8.699 | 0.003 |

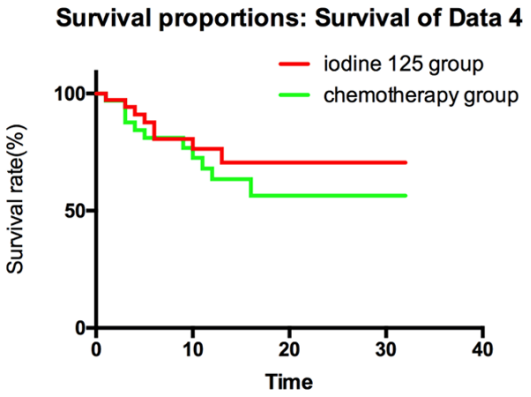


**Figure 4.** Comparison of 3-year survival rates.

seeds were used in the treatment of recurrent malignant tumors of the head and neck, showed that iodine-125 seed implantation not only provides satisfactory therapeutic effects after surgery, but also showed less adverse reactions [24]. In addition, another study described the advantages of iodine-125 seed implantation. Because iodine-125 has a shorter radiation range and a longer half-life, it can irradiate tumor cells continuously with low doses during the half-life period. Thus, it can also avoid damage to normal tissues, to a great extent. This may explain why iodine-125 seed implantation has minor adverse effects [25].

Finally, the current study compared 1-year progression-free survival and 3-year survival rates of the two groups, aiming to explore the prognostic impact of iodine-125 seed implantation in patients with ocular malignant tumors. One-year progression survival rate and 3-year survival rates were significantly higher in the iodine-125 group than in the chemotherapy group. This suggests that the use of iodine-125 seeds in patients with ocular malignant tumors can significantly improve patient prognosis. Previous studies have also shown that iodine-125 seed implantation can improve 5-year survival rates in patients with prostate cancer, as well as improving median survival times of patients with advanced pancreatic cancer, in accord with current findings [26, 27].

In summary, application of radioactive iodine-125 seed implantation for treatment of ocular malignant tumors can significantly improve therapeutic efficacy. It effectively reduces serum levels of tumor markers CEA and VEGF and improves 1-year progression-free survival and 3-year survival rates. In addition, iodine-125 seeds have high levels of safety. Thus, this method is worthy of promotion in clinical practice. However, a limitation of the current study was the lack of studies with similar research. This was possibly due to the relatively few studies on the application of iodine-125 seed implantation in ocular tumors. Moreover, the current study did not evaluate patient vision and eye appearances after treatment. Future studies will further explore the therapeutic effects of iodine-125 seed implantation, aiming to provide a more accurate theoretical basis for treatment of patients with ocular malignant tumors.

## Disclosure of conflict of interest

None.

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