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# Oncology Treatment Discovery

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2024, Volume 2, Issue 1

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http://ojs.bbwpublisher.com/index.php/OTD

# Analysis of the Effect of Ambulatory Chemotherapy (Portable Infusion Pump Use) Video Education on Knowledge, Self-efficacy, and Anxiety of Colorectal Cancer Patients

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**Abstract:** *Objective:* To analyze the effect of video education on ambulatory chemotherapy with a portable infusion pump on the knowledge, self-efficacy, and anxiety of colorectal cancer patients. *Methods:* This study employs a quasi-experimental study as a nonequivalent control group and a non-synchronized design. The 48 participants selected in this study were colorectal cancer patients who received chemotherapy with a portable infusion pump through an ambulatory care unit. Patient education was divided into printed materials and videos, and the patient's knowledge, self-efficacy, and anxiety were measured. Data were analyzed using independent *t*-test, paired *t*-test, and Wilcoxon's signed rank test. *Results:* In the video education group, the patient's knowledge ($Z = -4.09$, $P < 0.001$) and self-efficacy ($Z = -2.72$, $P = 0.012$) significantly increased after education, and anxiety significantly decreased ($Z = 2.24$, $P = 0.035$). However, there was no difference in knowledge ($t = 0.09$, $P = 0.931$), self-efficacy ($t = 1.22$, $P = 0.229$), and anxiety ($t = -1.16$, $P = 0.250$) between the two groups after education. *Conclusion:* To improve the quality of life of cancer patients, it is necessary to promote self-efficacy and reduce anxiety. The results of this study suggested that more diverse educational methods should be attempted to improve knowledge and self-efficacy and reduce anxiety in colorectal cancer patients.

**Keywords:** Anxiety; Chemotherapy; Colorectal cancer; Knowledge

**Online publication:** March 29, 2024

## 1. Introduction

### 1.1. The need for the study

Cancer is one of the top three causes of death in the Republic of Korea. The incidence of cancer increased steadily from 1999 to 2012, followed by a slight decrease until 2015. However, since 2016, the incidence of cancer increased again, and in 2019, the cancer incidence rate was 475.3 per 100,000 people. If Koreans reach a life expectancy of 83 years, the incidence of cancer is 37.4% (34.2% for women and 39.8% for men), where

colorectal cancer is the fourth most common cancer after thyroid, lung, and stomach cancers [1].

Looking at the trend of cancer mortality rates in Korea, colorectal cancer is the third leading cause of death after lung and liver cancer, with an increasing mortality rate. According to the World Health Organization's (WHO) Cancer Branch of the WHO's International Agency for Research on Cancer (IARC), the incidence of colorectal cancer in 186 countries in 2018 was 44.5 per 100,000 people. The incidence rate of colorectal cancer in the Republic of Korea was reported to be the second highest globally [1,2].

Chemotherapy is used as an adjuvant treatment after surgery in colorectal patients in some second and third-stage cases according to the National Comprehensive Cancer Network's (NCCN) Colorectal Cancer Guidelines, or as a curative treatment in stage IV of the disease. The chemotherapy drugs used for colorectal cancer are mainly FOLFOX (Folinic acid, 5-fluorouracil, and Oxaliplatin) and FOLFIRI (Folinic acid, 5-fluorouracil, and Irinotecan) in patients with metastatic colorectal cancer [3]. The FOLFOX and FOLFIRI chemotherapy regimen consists of 12 chemotherapy treatments given every 2 weeks for a total of 6 months [4].

Recently, hospitalization for chemotherapy has been shortened, and due to the patient's medical condition, cancer treatment can be performed through outpatient injection rooms or treatment centers. In this study, patients received chemotherapy for 5–6 hours, and at the end of the process, the patient was discharged with a portable chemotherapy (chemo) infusion pump [5]. While the portable chemo infusion pump offers patients economic and time-saving benefits of reducing hospitalization periods, there are concerns about the side effects of infusing chemotherapy drugs at home. This causes anxiety about patients not being able to take immediate action due to uncertainties and inexperience in managing infusers, along with the fluctuations in the end time of chemotherapy infusion due to the changes in temperature and viscosity of medications in different environments. Despite these drawbacks, the utilization of chemo infusion pumps is increasing due to their advantages. However, there is a lack of research measuring the cancer patient's knowledge of such devices whereby education on chemo infusion pumps is usually limited to printed materials distributed by medical device manufacturers [3,5].

The portable infuser is attached to the patient at the hospital and medication is administered by the patient at home until the infusion is complete. Patients need to be aware of how to manage the pump themselves and how to act in cases of unexpected side effects, unexpected changes to medications, or unexpected situations. Thus, patients need to have a sense of self-efficacy and follow the instructions [6]. Patient self-efficacy is a key factor in treatment adherence, reducing stress, and improving quality of life [7,8]. Higher self-efficacy is associated with a greater will to live, physical, emotional, and social functioning, along with better-coping mechanisms for dealing with cancer [9]. Social and emotional support is a key factor in fostering a sense of well-being. Adequate training of healthcare providers is important to provide such support to patients [6,9].

Anxiety in cancer patients is most often caused by uncertainty about treatment and prognosis and the psychological shock of being diagnosed with cancer. Anxiety has been linked to the patient's quality of life [10]. Patients require social, physical, and emotional support to reduce their anxiety [11]. Cancer patients undergoing chemotherapy may experience peripheral neuropathic pain and a variety of side effects, including nausea, vomiting, and increased levels of anxiety. Appropriate education about chemotherapy and cancer was reported to be effective in reducing anxiety [12,13].

Recently, outpatient and ambulatory cancer drug administration and the use of portable anti-cancer infusion devices have been popularized. Currently, only a small number of domestic and international studies have demonstrated the effectiveness of these devices and their impact on the overall quality of life for cancer patients [3,5,14,15]. In the oncology infusion rooms, oncology nurses provide education not only about chemotherapy but also on the use of portable chemo infusion pumps and coping strategies to manage symptoms

that may arise. However, there is a lack of research on the effectiveness of education regarding these portable chemo infusers. A previous study measured the knowledge of colorectal cancer patients through print and video education and found that video education was more effective than print education.

Based on the above, this study aimed to determine the effectiveness of video education on the training of using a portable chemo infusion pump in colorectal cancer patients [16].We also aimed to determine whether colorectal cancer patients possess knowledge of the Hugh substitute cancer infusion device, how to use it, and the necessary precautions in case of an emergency. We seek to assess the changes in participants' knowledge, self-efficacy, and anxiety through this intervention. This study can serve as a basis for developing a portable chemo infuser training program to enhance the patient's overall quality of life and ability to cope with cancer.

### 1.2. Purpose of the study

The purpose of this study is to determine the effectiveness of video training on portable chemo infusion devices on colorectal cancer patients' knowledge, self-efficacy, and anxiety.

The hypothesis to validate the effectiveness of the education program is as follows.

Hypothesis 1: The experimental group will use portable chemo infusers more than the control group and have higher knowledge regarding the device.

Hypothesis 2: The experimental group will have better self-efficacy than the control group.

Hypothesis 3: The experimental group will have less anxiety than the control group.

## 2. Research methods

### 2.1. Study design

This experimental group received handheld chemo injector video training, while the control group received traditional training using print materials. This was a quasi-experimental study that used a non-equivalent control group to compare the before and after results.

### 2.2. Study subjects

This study included patients with colorectal cancer diagnosed at G University Hospital in City I and who were receiving chemotherapy using portable chemo infusion pumps. The number of subjects was calculated using the G-power 3.1.9.4 program and calculated by a *t*-test, with a significance level of 0.05 and a power of 80%. A moderate effect size of 0.5 was chosen, which resulted in a minimum of 24 subjects per group. Considering a 20% dropout rate, 60 participants were selected with 30 per group. Six patients dropped out due to hospital transfer or personal reasons (3 in the control group, and 3 in the experimental group), leaving 48 participants in the final analysis, and 24 in each group. The first 30 people were selected as the control group in the order of their visits to the hospital. The experimental group received an enhanced video training program on the use of portable chemo infusers. The control group received conventional training via printed materials. Both groups were surveyed after the intervention.

### 2.3. Video training of portable chemo infuser

Video training on the portable chemo infusion pump was available through the research institute and was developed collaboratively by the principal investigator and other researchers. The video details the usage of the portable chemotherapy infusion pump, the location of the speed control, the impact on daily activities when using the device, the changes in the shape of the drug infusion over time, the operation of the portable anticancer infuser clamp, and the necessary precautions. Two post-operative specialists, a nursing professor, 5

head nurses in the chemotherapy ward, and 10 nursing staff were deployed to review the video's content.

Standard training for portable chemo infusers was provided by the manufacturer, which provided printed materials on how to use the portable chemo infusion device and the necessary precautions. When the experimental group visited the research center for anticancer treatment, they were shown the video for 9 minutes with a tablet, and an education session was conducted. The control group received traditional training with printouts and a brief explanation. Portable chemo infusion machine.

## 2.4. Research tools

### 2.4.1. Knowledge of portable anti-cancer infusers

The assessment of the level of knowledge was developed by the research team. The 10-item questionnaire covers the content of the video training (role and use of the portable chemo infusion pump). To validate the instrument's validity, 2 female nursing professors, one colorectal cancer nurse, and one cancer center and ambulatory center nurse were interviewed. We interviewed a total of 6 nurses, 3 with at least 5 years of ward experience. The Item-Content Validity Index (I-CVI) was rated on a scale of 1 for "not very relevant" to 4 for "very relevant." Items that received more than 80% of responses in the ratings of 3 and 4 were selected. The content validity coefficient was 0.95 and all 10 items in the initial construct were adopted. For each question, patients were asked to respond yes, no, or do not know, where 1 point for a correct answer and 0 points for an incorrect or do not know answer. The higher the score, the higher the level of knowledge. The instrument had a KR-20 value of 0.89.

The participants' self-efficacy was assessed by the Self-Management Resource Center, which provides chronic disease management resources for research without requiring approval [18]. The tool used was the Self-Efficacy for Managing Chronic Disease 6-item scale (SECD-6) translated by Kim *et al*. [19]. The tool consisted of 6 questions on a 10-point Likert scale, from 1 (not at all confident) to 10 (completely confident). The total score ranges from 6–60, with higher scores indicating higher self-efficacy. The reliability of the tool at the time of its development showed a Cronbach's α value of 0.91, and the reliability of this tool in this study was 0.96.

The participants' state of anxiety before and after the training program was measured using the State-Trait Anxiety Inventory by Spielberger, which was adapted by Kim et al. [20,21]. The side scale consisted of a total of 20 questions, answered on a 4-point Likert scale. The total score ranges from 20–80, with higher scores indicating higher levels of anxiety. The original scale had a Cronbach's α value of 0.97. In this study, the reliability of the scale was 0.97 and a Cronbach's α value of 0.83 was obtained.

## 2.5. Data collection

Data collection for this study took place from August 1, 2021, to September 1, 2021. This study was conducted for a total of 6 weeks, and the subjects included were colorectal cancer patients undergoing chemotherapy with a portable chemo infusion pump. The research protocol was explained to the participants and their written consent was obtained. Participant education was conducted in the consultation room of the outpatient treatment center of the institution. This study examined the treatment effect between the experimental and control groups. To control the spread of the treatment effect between both groups, the control group training was staggered by two weeks. The pre-and post-survey intervals between each group were two weeks. Details are shown in **Table 1**.

**Table 1.** Research design

| Group | Pretest | Intervention | Post-test | Pre-test | Intervention | Post-test |
|---|---|---|---|---|---|---|
| Experimental group ($n$ = 24) | | | | Ye1 | Xe | Ye2 |
| Control group ($n$ = 24) | Yc1 | X | Yc2 | | | |

Xe= Portable infusion pump video education; Ye1, Ye2, Yc1, Yc2= Knowledge, Self-efficacy, Anxiety

### 2.5.1 Preliminary research

In this study, the subjects were trained by a principal investigator and a co-investigator, and a questionnaire was administered before the start of the training to determine the general characteristics and knowledge level of the subjects. Self-efficacy and anxiety were measured using self-report measures.

### 2.5.2. Experimental treatment

The control group was provided with traditional printed materials. The experimental group was provided with video training of the portable chemo infusion pump along with the existing printouts.

### 2.5.3. Post-intervention

Two weeks after the intervention, when the subjects returned to the ambulatory care center, the post-test questionnaire was administered in the same way as the pretest questionnaire.

## 3. Data analysis methods

The collected data were analyzed using the IBM SPSS/WIN 22.0 (IBM Corp. Armonk, NY, USA) program. The general characteristics of the subjects were expressed as mean ± standard deviation, frequency, and %. The data were compared and analyzed using an independent $t$-test and the chi-squared ($\chi^2$) test to verify the homogeneity of the subjects. To compare the effectiveness of the experimental and control groups before and after the training, the normality was tested using the Shapiro-Wilk test. Anxiety scores were compared using a paired $t$-test. The knowledge scores were not normally distributed and were analyzed using paired $t$-test or Wilcoxon signed rank test. The differences between both groups after training were analyzed using an independent $t$-test. Results were considered statistically significant at $P < 0.05$.

## 4. Ethical considerations

The ethical aspects of the study were approved by the Institutional Review Board (IRB) of G University Hospital, Chihan, China. Ethical review approval (IRB: No. GFIRB2021-31). All patient data were kept confidential.

## 5. Findings

### 5.1. Verification of the general characteristics and homogeneity of both groups

The average age of the subjects in this study was 60.50 ± 9.09 years old, with a mean age of 62.3 ± 8.84 years for the control group and 58.67 ± 9.15 years for the experimental group. The control group consisted of 20 (83.3%) males and 4 (16.7%) females. The experimental group consisted of 16 (66.7%) males and 8 (33.3%) females. In terms of marital status, a majority of the subjects were married, followed by 6 (5.5%) who were widowed or divorced 6 (12.5%). Twenty subjects 20 (83.3%) in the control group and 15 (62.5%) subjects in

the experimental group were unemployed. In terms of education, 13 (54.2%) and 12 (50.0%) of the participants in the control group and experimental group had graduated from high school, respectively.

As for the metastasis status, 18 (75.0%) patients in the control group and 12 (50.0%) patients in the experimental group had metastasis. The mean number of chemotherapy treatments was 1.96 ± 1.00 times in the control group and 1.58 ± 0.58 times in the experimental group. The general characteristics of the experimental and control groups did not show statistically significant differences, confirming the homogeneity of the two groups ($P > 0.05$) Details are shown in **Table 2**.

**Table 2.** Differences in general characteristics between the two groups (mean ± standard deviation, [*n* (%)])

| Characteristics | Categories | Total (*n* = 48) | Control group (*n* = 24) | Experimental group (*n* = 24) | $\chi^2$ or *t*/*P* |
|---|---|---|---|---|---|
| Age (year) | | 60.50 ± 9.09 | 62.33 ± 8.83 | 58.67 ± 9.15 | -1.45 (0/165) |
| Gender | Male<br>Female | 36 (75.0)<br>12 (25.0) | 20 (83.3)<br>4 (16.7) | 16 (66.7)<br>8 (33.3) | 1.78 (0.182) |
| Marital status | Single<br>Married<br>Other | 1 (2.1)<br>41 (85.4)<br>6 (12.5) | 0 (0.0)<br>20 (83.3)<br>4 (16.7) | 1 (4.2)<br>21 (51.2)<br>2 (8.3) | 1.69 (0.429) |
| Job | Yes<br>No | 13 (27.1)<br>32 (66.7) | 4 (16.7)<br>20 (83.3) | 9 (37.5)<br>15 (62.5) | 2.61 (0.193) |
| Religion | Yes<br>No | 25 (54.2)<br>22 (45.8) | 10 (41.7)<br>14 (58.3) | 16 (66.7)<br>8 (33.3) | 3.02 (0.147) |
| Level of education | Elementary school<br>Middle school<br>High school<br>College | 6 (12.5)<br>8 (16.7)<br>25 (52.1)<br>9 (18.7) | 2 (8.3)<br>5 (20.8)<br>13 (54.2)<br>4 (16.7) | 4 (16.7)<br>3 (12.5)<br>12 (50.0)<br>5 (20.8) | 3.45 (0.485) |
| Metastasis | Yes<br>No | 30 (62.5)<br>18 (37.5) | 18 (75.0)<br>6 (25.0) | 12 (50.0)<br>12 (50.0) | 3.20 (0.074) |
| Number of chemotherapies | | 1.77 ± 0.83 | 1.96 ± 1.00 | 1.58 ± 0.58 | -1.56 (0.119) |

## 5.2. Validation of the homogeneity of the dependent variable

As shown in **Table 3**, the knowledge, self-efficacy, and anxiety did not differ between the experimental and control groups and homogeneity was confirmed ($P > 0.05$).

**Table 3.** Homogeneity of the dependent variable between the two groups (mean ± standard deviation, [*n* (%)])

| Variables | Control group (*n* = 24) | Experimental group (*n* = 24) | *t*/*P* |
|---|---|---|---|
| Knowledge (0–10) | 2.83 ± 2.93 | 1.92 ± 3.08 | -1.06 (0.296) |
| Self-efficacy (6–60) | 33.00 ± 13.44 | 34.83 ± 15.20 | 0.44 (0.660) |
| Anxiety (20–80) | 45.25 ± 8.06 | 44.79 ± 10.15 | -0.17 (0.863) |

## 5.3. Differences in the pre-and post-training knowledge, self-efficacy, and anxiety

As shown in **Table 4**, the knowledge and self-efficacy of the experimental group increased as compared to the control group, and the levels of anxiety decreased ($P < 0.05$).

**Table 4.** Differences in knowledge, self-efficacy, and anxiety score before and after education (mean ± standard deviation, [*n* (%)])

| Variables | Categories | Control group (*n* = 24) | Experimental group (*n* = 24) | *t*/*P* |
|---|---|---|---|---|
| Knowledge | Pre-test | 2.83 ± 2.93 | 1.92 ± 3.08 | 0.09 (0.931) |
| | Post-test | 7.92 ± 2.00 | 7.96 ± 1.23 | |
| | Difference | 5.09 | 6.04 | |
| | *P* | -4.00 (< 0.001) | -4.09 (< 0.001) | |
| Self-efficacy | Pre-test | 33.00 ± 13.44 | 34.83 ± 15.20 | 1.22 (0.229) |
| | Post-test | 36.21 ± 13.98 | 40.54 ± 10.39 | |
| | Difference | 3.21 | 5.71 | |
| | *P* | -1.63 (0.116) | -2.72 (0.012) | |
| Anxiety | Pre-test | 45.25 ± 8.06 | 44.79 ± 10.15 | -1.16 (0.250) |
| | Post-test | 43.67 ± 8.86 | 41.08 ± 6.30 | |
| | Difference | -1.58 | -3.71 | |
| | *P* | 1.17 (0.256) | 2.24 (0.035) | |

## 6. Discussion

It is reported that 80%–90% of all cancer patients will receive chemotherapy at least once in their lifetime. For colorectal cancer patients, FOLFOX and FOLFIRI are two of the most commonly used chemotherapy drugs [3]. Recently, many healthcare organizations have been offering chemotherapy at outpatient and ambulatory treatment centers because of the economic and time benefits advantages. In addition, the use of portable chemotherapy infusion devices has led to high patient satisfaction and is cost-effective [4].

Training on the usage of portable chemo infusion pumps has traditionally been provided through printed materials distributed by manufacturers. These teaching methods are simple and time-saving, but there was no way to assess how well patients understood and retained the content. In this study, the content of the printed materials was modified and improved to make them more interesting and understandable. A researcher was assigned to produce and distribute the video educator materials.

This study found that both groups showed improvements in knowledge and self-efficacy and had decreased anxiety, but the difference in the post-training scores of these variables was significantly different. In the experimental group, the level of knowledge increased from 1.92 to 7.96 and the self-efficacy improved from 34.83 to 40.54 post-intervention. In addition, anxiety decreased from 44.79 to 41.08 post-intervention. This is because print education has always been a convenient and easy way for healthcare providers but the patient's level of knowledge, self-efficacy, and anxiety are taken into account. It was noted that the video training method increased the knowledge level of the subjects and was convenient, highlighting the significance of this study.

The video training and knowledge measures used in this study are not comparable. While direct comparisons are difficult to make due to the lack of prior research, several studies have been conducted in cancer and colorectal cancer patients, hence we will discuss how this study compares to other studies on education, self-efficacy, and anxiety in cancer patients and colorectal cancer patients. The knowledge level of the subjects about the portable chemo infusion device showed significant changes between both groups, however, there was no difference between both groups. This is similar to the results of Meade, who measured the knowledge level of colorectal cancer patients after education using various media [16] and found no difference in the knowledge level of the two groups.

This indicates that the instructions given to the audience should be organized in a way that considers the intellectual and comprehension abilities of the patients. In this study, most of the subjects had a high school-

level education or higher. The number of subjects was small, making it difficult to conduct a proper assessment. Therefore, it is unlikely that there was a difference in the level of knowledge across the two teaching methods. Future research should focus on developing training programs for the use of portable chemo infusers catered for different ages and education levels. In addition, in this study, patients were only taught the theoretical content but did not practice it. In future studies, it is recommended to incorporate a hands-on component to measure the extent of knowledge gains.

The self-efficacy in the experimental group was significantly different before and after training ($t$ = -2.72, $P$ = 0.012). Self-efficacy is reported to be an important influencer of cancer survivorship in cancer patients and is a significant predictor of health behaviors and self-care activities [16]. Good self-efficacy has also been shown to improve the quality of life for cancer patients and positively impact their resilience [8]. This was similar to the results of Lee *et al*. who measured self-efficacy after implementing an integrated education program involving multidisciplinary professionals for breast cancer patients [22]. Additionally, the results correlated to a study by Tokdemir and Kav that examined patient self-efficacy in cancer patients receiving oral anticancer medications with specialized education on oral anticancer medications [23]. These results suggest that self-efficacy is dependent on one's knowledge and abilities and that improving one's knowledge through video training will improve one's self-efficacy [24]. Therefore, appropriate education will increase the knowledge and self-care behaviors of cancer patients, which will enhance their self-efficacy and thus improve their quality of life [6,9].

In this study, the experimental group showed a significant difference in pre- and post-training self-efficacy, but there was no difference in post-training self-efficacy between both groups. This is likely due to the small number of subjects and the frequency of training. A study by Merluzzi2 showed that regular training has a significant effect on improving self-efficacy in cancer patients [24]. Future studies will need to verify the effectiveness of providing regular training instead of one-time training. The patients' anxiety levels in the experimental group also showed a significant difference before and after training ($t$ = 2.24, $P$ = 0.035). Anxiety has been categorized as a quality-of-life impairment for colorectal cancer patients and is a psychological condition that many cancer patients experience throughout treatment, from diagnosis to chemotherapy [10,25,26]. Anxiety in cancer patients is one of the symptoms that must be controlled and many variables have been reported to influence anxiety, including cancer stage, education, and number of chemotherapy treatments [26–29]. In addition, Kim *et al*. reported that direct and indirect contact between healthcare providers and cancer patients, such as communication and nursing care, was reported to reduce anxiety in cancer patients [28]. Regular education and communication are effective in improving patients' self-efficacy and anxiety. Therefore, it is necessary to develop education programs that cover variables such as cancer stage, number of chemotherapy treatments, and education level to control anxiety in cancer patients. However, 62.5% of the subjects in this study were limited to stage 4 cancer patients with metastasis with high anxiety levels. Future follow-up studies should measure the effectiveness of education for cancer patients at various stages. Besides that, this study also did not include content aimed at reducing anxiety during training, which may explain the lack of differences between groups. Therefore, we recommend that future studies include interventions such as emotional support and deep breathing techniques to reduce anxiety.

As this study utilized a convenience sample from a single medical center, it is difficult to extrapolate the findings to bigger populations. Furthermore, we were unable to identify differences between groups due to the small number of subjects and the frequency of training, hence future studies should include a larger number of patients and conduct regular training to measure the effects of different training methods and the frequency of training. This study only examined self-efficacy and anxiety as psychosocial variables in cancer patients. As many psychosocial variables affect cancer patients, it is recommended that future studies examine a variety of

these variables to identify factors that positively affect the quality of life and prognosis of cancer patients. In addition, this study did not include training on improving self-efficacy and anxiety because the training was only on the use of portable chemo infusion devices. Future studies should include training on self-efficacy and anxiety to measure the effect of training on these variables.

## 7. Conclusion

Education via video and handprinted materials both improved the patient's knowledge regarding the use of portable chemo infusion pumps. However, the experimental group that received video experienced significant improvement in their knowledge, and self-efficacy, and experienced reduced anxiety as compared to those of the control group. Although the difference between the groups was not significant, based on the improvement of self-efficacy and reduction of anxiety in the group that received the video training program, it is recommended to develop various new training methods regarding the correct use of portable chemotherapy infusion machines.

## Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Analysis of the Effects of the Addition and Subtraction Therapy of Jianpi Jiedu Decoction on T-lymphocyte Subpopulations' Changes in Colorectal Cancer Patients' Clinical Symptoms

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**Abstract:** *Objective:* To investigate the clinical efficacy of applying the addition and subtraction of Jianpi Jiedu decoction (JPJD) in patients suffering from colorectal cancer and changes in their clinical symptoms. *Methods:* Seventy-two colorectal cancer cases were selected and randomly divided into the control group and the observation group, where both groups received the same comprehensive treatment and chemotherapy intervention after surgery. The observation group received the addition and subtraction therapy of JPJD based on the control group. The Chinese medicine (TCM) symptom scores, the intestinal bacterial flora, and the changes in the T-lymphocyte subsets of the two groups were compared. *Results:* The observation group had lower TCM evidence points, more *Escherichia coli*, less Bifidobacterium and Lactobacillus, and higher T-lymphocyte subpopulation levels than that of the control group after treatment ($P < 0.05$). *Conclusion:* The application of addition and subtraction therapy of JPJD in conjunction with postoperative radiotherapy for colorectal cancer patients further improved the patient's clinical symptoms and intestinal flora environment, and effectively enhanced their immunity. which is worthy of promotion.

**Keywords:** Jianpi Jiedu formula; Colorectal cancer; Clinical symptoms; T-lymphocyte subpopulation

**Online publication:** March 29, 2024

## 1. Introduction

Colorectal cancer is the collective name of colon cancer and rectal cancer. It is a highly prevalent malignant tumor in China with a relatively high fatality rate of about 20% [1]. Currently, surgery with adjuvant radiotherapy is the optimal treatment plan for colorectal cancer. When combined with postoperative radiotherapy, it can continuously inhibit the proliferation of tumors, thus increasing the patient's chance of survival. However, both the invasive damage caused by surgery and a series of toxic side effects caused by radiotherapy can adversely impact the internal environment of the gastrointestinal tract and further exacerbate the symptoms of spleen deficiency. Subsequently, these symptoms prompt a continuous decline in the body's immune system, and

if not effectively intervened promptly, will hinder the recovery process of the patients. In severe cases, the disease may recur again [2]. From the perspective of traditional Chinese medicine (TCM), colorectal cancer is categorized as "blood in stool," "dirty poison," etc. Its occurrence is related to the accumulation of dampness and toxins in the intestines caused by dietary irregularities, emotional disorders, and a weak spleen. Surgery can further exacerbate fluid loss and deplete qi, resulting in the loss of a balanced gastric function. This complicates the production of qi and intestinal bacterial flora, increasing the risk of recurrence [2]. Therefore, this study focused on applying Jianpi Jiedu decoction (JPJD) with additions and subtractions to investigate its effectiveness in treating colorectal cancer patients. 72 cases have been selected as the study subjects. The details have been described in the following [3].

## 2. Information and methods

### 2.1. Data

Seventy-two patients with colorectal cancer who were admitted from February 2020 to May 2023 were selected and grouped into a control group and an observation group, with 36 cases each. The control group consisted of 25 males and 11 females aged 48–84 years old, with an average of 66.35 ± 8.92 years. The duration of the disease was 1–6 years, with a mean duration of 3.02 ± 1.21 years. The clinical staging of Stage II: Stage III: Stage IV was in the ratio of 14:20:2. There were 19 and 17 cases of colon cancer and rectal cancer, respectively. The observation group consisted of 24 males and 12 females aged 46–85 years old, with an average age of 65.96 ± 8.84 years. The disease duration was 1–5 years, with a mean duration of 2.99 ± 1.18 years. The clinical staging of Stage II: Stage III: Stage IV was in the ratio of 12:21:3. There were 17 and 9 cases of colon cancer and rectal cancer, respectively. The data between the groups were not significantly different after normalized comparison ($P > 0.05$).

Inclusion criteria: (1) Satisfy the relevant diagnostic criteria of the Chinese Diagnostic and Therapeutic Criteria for Colorectal Cancer (2017 Edition) [4] and the Guidelines for Clinical Research of New Chinese Medicines (for Trial Implementation) [5]; (2) obtained a score of more than 60 in the Kahn's Functional Status Scale (KPS); (3) meet the relevant therapeutic indications of surgery, postoperative radiotherapy, and chemotherapy; (4) have an expected survival time of ≥ 6 months; (5) able to communicate normally; (6) consented. Exclusion criteria: (1) Pregnant and lactating women; (2) distant metastasis; (3) presence of other malignant tumors; (4) hematologic and immune system diseases; (5) serious dysfunction of heart, brain, kidney, and other important organs; (6) contraindications to surgery, radiotherapy, and chemotherapy; (7) intolerance or allergy to the study drugs; (8) low compliance; (9) dropped out of the study halfway.

### 2.2. Methods

After both groups were admitted to the department, surgical treatment was carried out by the same medical team, and postoperative interventions such as anti-infection, nutritional support, gastrointestinal decompression, etc. were implemented according to the specific conditions of the patients, based on the CapeOX chemotherapy program that was carried out in the two groups. For the control group, on the first postoperative day, 130 mg/m$^2$ oxaliplatin (injectable preparation, State Drug License: H20094158, Manufacturer: Yangzijiang Pharmaceutical Group Co. Group Co., Ltd, specification: 50 mg) was used for intravenous drip treatment. On the 1$^{st}$ to 14th day, 1000 mg/m$^2$ capecitabine (tablets, State Drug License: H20133361, manufacturer: Qilu Pharmaceutical Co., Ltd, specification: 500 mg) was taken orally twice daily and the treatment was continued for 3 weeks. The observation group was given the addition and subtraction therapy of JPJD based on the control group. The JPJD decoction consisted of *Astragalus membranaceus* (30 g), Hedyotis diffusa (30 g), dandelion (25 g), Coix

lacryma-jobi (20 g), *Semen coicis* (20 g), *Cynanchum paniculatum* (15 g), fried atractylodes macrocephala (12 g), Poria (12 g), chenpi (6 g), with the addition and subtraction of ingredients according to the disease. For abdominal distension, 12 g of *Citrus sinensis* shells was added; for abdominal pain, 12 g *Corydalis yanhuosuo* was added; for those with loose stool, 12 g *Rhizoma atractylodis* was added. Every day, 800 mL water was added to 1 dose of the prescription decocted until 300 mL, where it was then taken twice a day, 150 mL each time, with warm water for 3 weeks.

### 2.3. Observation indicators

(1) TCM symptom points

Based on the Guiding Principles for Clinical Research of New Chinese Medicines, points were allocated to the primary symptoms (night sweats, nausea, tiredness of limbs) and secondary symptoms (intestinal sounding, abdominal distension, belching) of the two groups. The primary symptoms were given points of 0, 2, 4, and 6 according to the sequence of "none, mild, moderate, and severe," and the secondary symptoms were given points of 0, 1, 2, and 3 according to the same sequence. The points corresponded to the severity of the related symptoms.

(2) Intestinal flora

Before and after the implementation of the treatment plan, 0.5 g of fresh feces was collected from both groups and placed on a culture medium, and the QXC-500 automatic colony counter was applied to detect the specific number of *Escherichia coli*, Bifidobacteria, and Lactobacillus.

(3) T-lymphocyte subpopulation level

Before and after the therapeutic matters were carried out, 5 mL of fasting venous blood was extracted from both groups, and the specific values of CD3+, CD4+, and CD4+/CD8+ were measured by enzyme-linked immunosorbent assay.

### 2.4. Statistical analysis

Based on the SPSS 25.0 for Windows software, the observed data were compared normatively. The measurement data were expressed as mean ± standard deviation and compared using the *t*-test. Count data were expressed as % and analyzed using the chi-squared ($\chi^2$) test. Results were considered statistically significant at $P < 0.05$.

## 3. Results

### 3.1. Comparison of Chinese medicine symptoms points between the two groups

As shown in **Table 1**, the TCM symptom points of the two groups before treatment were compared, and there was no difference ($P > 0.05$). The total TCM symptom points of the observation group were significantly lower than those of the control group after the treatment ($P < 0.05$).

### 3.2. Comparison of intestinal flora between the two groups

As shown in **Table 2**, after treatment, the number of *Escherichia coli* in the observation group was significantly higher than that of the control group, and the number of bifidobacteria and lactobacilli was significantly lower than that of the control group ($P < 0.05$).

### 3.3. Comparison of T-lymphocyte subpopulation levels between the two groups

As shown in **Table 3,** after treatment, the T-lymphocyte subpopulation levels of the observation group were significantly higher than those of the control group ($P < 0.05$).

**Table 1.** Comparison of the observed results of TCM evidence points (mean ± standard deviation, points)

| Group | Period | Primary symptoms | Secondary symptoms | Total points |
|---|---|---|---|---|
| Control group ($n$ = 36) | Before treatment | 14.05 ± 5.28 | 6.96 ± 2.15 | 21.06 ± 8.46 |
| | After treatment | 8.25 ± 2.69 | 3.85 ± 0.92 | 12.21 ± 4.89 |
| Observation group ($n$ = 36) | Before treatment | 13.96 ± 5.20 | 6.85 ± 2.09 | 20.54 ± 8.29 |
| | After treatment | 4.69 ± 1.74 | 1.85 ± 0.36 | 6.58 ± 1.88 |
| $t$ | Before treatment | 0.073 | 0.220 | 0.263 |
| | After treatment | 6.667 | 12.147 | 6.448 |
| $P$ | Before treatment | 0.942 | 0.826 | 0.793 |
| | After treatment | 0.001 | 0.001 | 0.001 |

**Table 2.** Comparison of intestinal flora between the two groups (mean ± standard deviation, logCFU/g)

| Group | Period | *Escherichia coli* | Bifidobacterium | Lactic acid bacteria |
|---|---|---|---|---|
| Control group ($n$ = 36) | Before treatment | 7.56 ± 2.56 | 8.55 ± 3.56 | 8.28 ± 3.24 |
| | After treatment | 7.92 ± 3.22 | 7.59 ± 2.58 | 6.54 ± 2.18 |
| Observation group ($n$ = 36) | Before treatment | 7.59 ± 2.58 | 8.49 ± 3.49 | 8.30 ± 3.28 |
| | After treatment | 9.74 ± 4.11 | 5.01 ± 1.45 | 5.12 ± 1.51 |
| $t$ | Before treatment | 0.050 | 0.072 | 0.026 |
| | After treatment | 2.091 | 5.231 | 3.213 |
| $P$ | Before treatment | 0.961 | 0.943 | 0.979 |
| | After treatment | 0.040 | 0.001 | 0.002 |

**Table 3.** Comparison of T-lymphocyte subpopulations between the two groups (mean ± standard deviation)

| Group | Period | CD3+ (%) | CD4+ (%) | CD4+/CD8+ |
|---|---|---|---|---|
| Control group ($n$ = 36) | Before treatment | 51.95 ± **5.45** | 37.11 ± **2.98** | 1.31 ± 0.28 |
| | After treatment | 53.85 ± **7.69** | 39.38 ± **4.25** | 1.42 ± 0.51 |
| Observation group ($n$ = 36) | Before treatment | 52.01 ± **5.49** | 37.18 ± **3.02** | 1.34 ± 0.30 |
| | After treatment | 58.62 ± **9.68** | 42.12 ± **5.89** | 1.78 ± 0.79 |
| $t$ | Before treatment | 0.047 | 0.099 | 0.439 |
| | After treatment | 2.315 | 2.263 | 2.297 |
| $P$ | Before treatment | 0.963 | 0.921 | 0.662 |
| | After treatment | 0.024 | 0.027 | 0.025 |

## 4. Discussion

The occurrence of colorectal cancer is related to many factors, including chronic inflammation of the colon, adenoma or heredity, environment, and poor dietary habits (high-fat and low-fiber diet). During the initial stages, patients usually do not exhibit obvious symptoms and some of them only have slight indigestion or fecal occult blood. However, with the continuous enlargement of the tumor, or even infiltration and distant

metastasis, it can cause abdominal mass, abdominal pain, bloody stool, intestinal obstruction, fever, emaciation, anemia, and other symptoms. At the same time, the corresponding clinical symptoms can be triggered according to the organs involved in the lesion [6]. Surgery is one of the most intuitive and effective interventions for colorectal cancer, which can remove lesions to prevent the continuous progress of the disease. When combined with postoperative chemotherapy programs, it can greatly reduce the risk of disease recurrence and improve the patient's quality of life. Nonetheless, the disease has already caused different degrees of damage to the patient's gastrointestinal system and immune function. If coupled with the stressful trauma of surgery and the toxic side effects of chemotherapy, it may lead to gastrointestinal dysfunction such as tinnitus and abdominal distension, as well as complications such as infections and cystitis, thus greatly reducing the effectiveness of the clinical treatment. Therefore, it is necessary to focus medication usage on improving the clinical symptoms and promoting the recovery of gastrointestinal function [7].

This study showed that the observation group had lower TCM symptom scores and higher levels of intestinal flora and T-lymphocyte subpopulations than the control group, suggesting that the formula of JPJD can help accelerate the improvement of clinical symptoms and immune function. *Vincetoxicum paniculatum* can play the role of clearing heat and removing toxins by acting as an analgesic and expectorant; *Coix lacryma* and *Semen Coicis* can work together to detoxify the liver and stomach, clear heat, and dry dampness; chenpi can regulate qi, tonify the spleen, and dry dampness to strengthen the spleen and eliminate toxins [8,9]. Qiu showed that the JPJD decoction effectively inhibited the mRNA expression of the lesion through mitogen-activated protein kinases (MAPK) and P13K-Akt signaling pathways to regulate the tumor microenvironment better and inhibit the proliferation and metastasis of the tumor cells [10].

## 5. Conclusion

The application of JPJD in conjunction with postoperative chemotherapy in colorectal cancer patients helped improve their clinical symptoms, intestinal microecology, and immune function. It is recommended to be vigorously promoted.

## Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Analysis of the Treatment for Advanced Microsatellite Stable Colorectal Cancer in Middle-Aged and Elderly People

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**Abstract:** Microsatellite stabilized (MSS) rectal cancer is a highly prevalent cancer in the middle-aged and elderly population. There exists some expertise in detecting and evaluating the chemotherapy effect in advanced colorectal cancer patients. Multiple studies have combined targeted therapy, chemotherapy, and immunotherapy as a breakthrough. Programmed cell death protein 1 (PD-1) inhibitors have certain therapeutic effects in the treatment of MSS rectal cancer patients. The combination of PD-1 inhibitors and furoquinib can improve the disease control rate (DCR) and progression-free survival (PFS) in colorectal cancer (CRC) patients with advanced MSS, and the adverse reactions are controllable. The combination of erlotinib hydrochloride and Xindilizumab was more effective in treating MSS-type colorectal cancer patients than clinical standard treatment. This study analyzes the various treatment methods for MSS-type CRC in middle-aged and elderly people to provide a reference basis in clinical practice.

**Keywords:** Microsatellite stability (MSS); Colorectal cancer; immunotherapy

**Online publication:** March 29, 2024

## 1. Introduction

Microsatellite stabilized (MSS) rectal cancer is a common molecular subtype of middle-aged and elderly rectal cancer and has attracted the attention of many researchers [1–3], with a moderate malignancy. MSS rectal cancer is sensitive to chemotherapy, resulting in a better overall prognosis for patients. In 2020, there were approximately 1.9 million new cases of cancer worldwide, with colorectal cancer (CRC) accounting for 10% of the total number of cancer cases, ranking third among all cancers and second in mortality rate. The clinical symptoms of colorectal cancer appear relatively late and about 85% of patients are already in the middle and late stages at the time of disease diagnosis [4,5].

## 2. Assessment and detection of microsatellite stable colorectal cancer

Hu conducted a study involving 200 patients with advanced colorectal cancer and treated them with the FOLFOX (folinic acid, fluorouracil, and oxaliplatin) chemotherapy regimen [6]. All primary tumor tissues from these patients were tested with DNA mismatch repair gene (MMR). The patients were then classified into two groups based on their microsatellite instability analysis results: the MSS group and the microsatellite instability (MSI) group. A retrospective analysis was performed to compare the clinical characteristics and chemotherapy efficacy between these two groups. In a study comparing these two groups of CRC patients, no statistically significant differences in age and gender were found. However, significant differences were observed in tumor location, pathological type, degree of differentiation, and metastasis status. The MSI group demonstrated a substantially lower disease control rate compared to the MSS group. MSI status has been identified as a crucial factor influencing chemotherapy efficacy and prognosis in late-stage CRC, making it a potential predictor for these outcomes. Wang collected primary tumor tissues from 181 patients with late-stage CRC [7]. Immunohistochemical testing was conducted to assess the expression of four proteins: MSH2, MSH6, MLH1, and PMS2 in these tissues. The patients were subsequently divided into MSI and MSS groups, and the differences in chemotherapy sensitivity and prognosis were analyzed. Although the MSI status did not correlate with overall survival time in late-stage CRC patients, it was significantly associated with the disease control rate, indicating its importance in evaluating the effectiveness of chemotherapy. In another study, Wu employed immunohistochemical methods to examine 41 CRC tumors [8]. A pathological slice scanner was utilized to count cells and measure CD68+ and CD163+ expression in atypical hyperplasia (AH) tissues located 5 cm (M5) and 10 cm (M10) adjacent to the tumor. The findings revealed a higher expression of CD68+ and CD163+ in the stromal tissues of colorectal cancer tumors as compared to adjacent non-cancerous tissues. No correlation was observed between their expression in tumors and AH tissues. Notably, CD163+ expression in tumors was associated with mutations in the Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene.

Cheng performed a retrospective analysis on 154 patients undergoing palliative chemotherapy for metastatic colorectal cancer [9]. The study involved using immunohistochemistry to detect the expression of mismatch repair (MMR) genes: MSH2, MLH1, PMS2, and MSH6 proteins in tumor tissues. The analysis focused on the relationship between MSI and various factors such as clinical features, chemotherapy response, and prognosis. The findings showed that the non-progression survival rate was significantly higher in the MSI-H group (85.71%) compared to the MSS group (57.86%), suggesting a pivotal role of MSI in influencing chemotherapy efficacy and prognosis in mCRC patients. The study underscores the necessity of routine MSI-H testing in this context. Wu collected primary tumor tissues from patients with stage IV intestinal cancer who were treated with either FOLFOX or XELOX (oxaliplatin and capecitabine) as their first-line chemotherapy regimen [10]. Immunohistochemistry was used to detect the expression of MMR genes: hMSH6, hPMS2, hMLH1, and hMSH2 proteins in these tissues. The study aimed to evaluate the relationship between the microsatellite status and the patient's clinical characteristics, prognosis, and chemotherapy response. Among the 79 patients who underwent palliative resection of the primary lesion, those with MSI exhibited a significantly longer median progression-free survival (PFS) compared to those with MSS. In patients with stage IV colorectal cancer who underwent palliative resection of the primary tumor, a positive correlation was observed between MSI status and both the DCR and PFS from chemotherapy. This finding emphasizes the importance of conducting microsatellite testing in mCRC patients.

## 3. Exploring treatment approaches for MSS CRC

### 3.1. Evaluating the efficacy of PD-1 inhibitors in treating MSS CRC

Zhu reported that multiple clinical trials have shown certain effectiveness in immunotherapy combined with targeted chemotherapy for KRAS mutated microsatellite stable mCRC [11]. Zhou found that the addition of PD-1 inhibitors to the treatment process of MSS-type CRC patients improved the immune status and levels of angiogenic factors in the body, which was beneficial for improving patient efficacy [12]. The use of PD-1 inhibitors was also safe. Rosixi found that the combination of Regorafenib and PD-1 inhibitors as a third line or higher treatment for advanced MSS type CRC may be more effective in PFS [13]. Li found that the combination of PD-1 inhibitors and furoquinib can improve the DCR and PFS of CRC patients with advanced MSS, with controllable adverse reactions [14]. Jia retrospectively analyzed the clinical data of 41 patients with MSS- or pMMR-type mCRC [15]. Patients who received third-line or above treatment with fruqintinib monotherapy or a combination of fruqintinib and PD-1 inhibitors were found to exhibit better clinical effects on MSS- or pMMR-type mCRC, and the combination therapy did not significantly increase toxicity.

### 3.2. The efficacy of alternative combination therapies in treating MSS CRC

Yu conducted a retrospective analysis of clinical data from 40 patients with inoperable MSS CRC [16]. The patients were evenly split into a control group and an observation group, each comprising 20 patients, based on their respective treatment protocols. The control group received XELOX chemotherapy combined with apatinib, whereas the observation group was treated with XELOX combined with apatinib and carrelizumab over a 6-week continuous period. The study measured the disease control rate, progression-free survival, objective response rate, overall survival, and adverse events of both groups. The results demonstrated that the combination of XELOX chemotherapy with apatinib and carrelizumab in treating inoperable metastatic MSS CRC was as effective as the combination of XELOX with apatinib alone. However, it showed superior results in terms of tumor objective response rate (ORR), PFS, and overall survival (OS), while maintaining a manageable safety profile. Sun focused on hospitalized CRC patients who underwent integrated treatment combining traditional Chinese and Western medicine, particularly those who had experienced first to third-line treatments in advanced stages [17]. The study collected information including disease specifics, treatment protocols, the start and failure times of each treatment stage, and traditional Chinese medicine (TCM) diagnoses from medical records. Descriptive statistics were used for the analysis and the Kaplan-Meier analysis was used to assess the third-line PFS of patients with various disease specifics and treatment regimens. Further, multivariate Cox regression analysis was used to identify key influencing factors. The findings suggested that the integration of traditional Chinese and Western medicine in the third-line treatment of advanced CRC might enhance patient survival, with benefits linked to TCM diagnostic types and the status of genetic testing. Ma conducted a retrospective analysis of the clinical data of 36 patients with advanced CRC [18]. These patients were divided into two groups based on their microsatellite status: MSI-H and MSS. All patients underwent treatment with carrelizumab combined with apatinib. The study compared the two groups in terms of mean PFS, DCR, ORR, and adverse reactions. Results showed that the combination of carrelizumab and apatinib was effective in advanced CRC patients who had not responded to second-line or higher treatments, with MSI-H CRC patients experiencing more significant benefits than MSS patients. Gi investigated a complex case of a patient with multiple metastatic rectal cancer (MSS with NRAS gene mutation) who also suffered from acute intestinal obstruction [19]. After the failure of second-line chemotherapy, the patient was treated with Regorafenib as a targeted therapy. Despite the progression of some lesions, the disease was controlled following the introduction of combined PD-1 inhibitor treatment. Notably, from the onset of third-line treatment, the patient primarily received home-based care. This approach significantly improved the patient's treatment compliance and safety, offering valuable insights into the clinical

management of patients with similar conditions.

In Zhu's study, 76 patients with late-stage colon cancer were randomly divided into two groups of 38 each: a control group treated with fruquintinib, and an observation group receiving a combination of sintilimab and fruquintinib [20]. After 6 months of treatment, it was observed that the efficacy of fruquintinib monotherapy was less effective compared to the combined treatment with sintilimab in MSS late-stage colon cancer. The combination treatment showed a minor impact on immune function and was well-tolerated by patients, indicating its potential application value in clinical settings. Ji focused on 30 patients with MSS CRC, dividing them into a control group, which received oral anlotinib hydrochloride capsules, and an observation group, treated with intravenous sintilimab injections in addition to anlotinib [21]. After 6 months, the clinical efficacy was evaluated using parameters such as ORR, DCR, complete tumor response (CR), partial tumor response (PR), stable disease (SD), and progressive disease (PD). Adverse drug reactions were assessed using the Common Adverse Reaction Event Criteria 4.2, and the patient's quality of life was evaluated using a cancer patient-specific scoring system. The study found that the combination of anlotinib hydrochloride and sintilimab improved the clinical efficacy and quality of life in MSS CRC patients with manageable adverse reactions.

## 4. Discussion

CRC is one of the common malignant tumors in middle-aged and elderly people. Previously, only approved drugs could be considered for the third-line treatment of advanced CRC. Targeted therapy research mainly focuses on molecular targets that inhibit tumor growth and proliferation. Among them, anti-vascular endothelial growth factor receptor drugs and anti-epidermal growth factor receptor drugs were the basic choices for the third-line treatment of advanced CRC. The MSI status is closely related to the chemotherapy efficacy and prognosis of advanced CRC and can be used as an indicator for predicting chemotherapy efficacy and prognosis in advanced CRC and routine MSI-H testing is necessary. CD68+ and CD163+ are highly expressed in the stroma of colorectal cancer tumors, and the expression of CD163+ in tumors is correlated with KRAS gene mutations.

## 5. Conclusion

The addition of PD-1 inhibitors to the treatment process of MSS CRC improved the immune status and angiogenic factor levels of the body, which was beneficial for enhancing the efficacy of patient treatment. The combination of Regorafenib and PD-1 inhibitors as a third line or higher treatment for advanced MSS-type CRC may be more effective in PFS. The combination of PD-1 inhibitors and furoquinib can improve DCR and PFS in CRC patients with advanced MSS, and the adverse reactions are controllable. The combination of XELOX chemotherapy with apatinib and calerizumab had a significant effect on non-surgical metastatic MSS-type CRC patients. The combination of carolizumab and apatinib regimen has potential efficacy and controllable adverse reactions in advanced CRC patients who have failed second-line or above treatment. The combination of xindilizumab and furoquinib had a relatively small impact on the immune function of patients and has potential application value. The clinical efficacy of the combination of enrotinib hydrochloride and xindilizumab in the treatment of MSS-type CRC patients after standard treatment failure was good, and the adverse reactions were controllable.

## Funding

Observation And Comparison of Therapeutic Effects of High-Dose Vitamin C Combined with Anti Vascular Targeted Drugs and Immunotherapy on MSS-Type Advanced Colorectal Cancer Patients, Shaoxing University,

School Level Project Y20220819

## Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Analysis of the Value of Ultrasound Imaging Combined with Serum Indicators in Evaluating the Invasiveness of Papillary Thyroid Carcinoma

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**Abstract:** *Objective:* To analyze the value of ultrasound imaging combined with serum indicators in evaluating the invasiveness of papillary thyroid cancer (PTC). *Methods:* One hundred and fifty patients with papillary thyroid cancer admitted to our hospital from September 2019 to December 2022 were selected. Pathological tissue testing was performed on all patients. According to the size, shape, boundary, internal echo, and characteristics such as microcalcification, the patients were divided into the PTC metastasis group ($n$ = 55) and the PTC group ($n$ = 95). The detection rate of ultrasound imaging combined with serum indicators and the invasiveness of PTC were observed and analyzed. *Results:* The detection rate of ultrasound imaging combined with serum indicators in both groups was significantly better than that of ultrasound imaging and serum indicators ($P < 0.05$). The detection rate of ultrasound imaging combined with serum indicators was compared between the groups. The removal rate of the PTC metastasis group was significantly better than that of the PTC group ($P < 0.05$). The levels of thyroid-stimulating hormone (TSH), thyroglobulin (Tg), thyroglobulin antibodies (TgAb), and thyroid autoantibodies (TPOAb) in the PTC group were lower than those of the PTC metastasis group ($P < 0.05$). *Conclusion:* Ultrasound imaging combined with serum indicators like TSH, Tg, TgAb, and TPOAb has important clinical significance in evaluating the invasiveness of PTC.

**Keywords:** Ultrasound imaging; Serum indicators; Papillary thyroid carcinoma

**Online publication:** March 29, 2024

## 1. Introduction

Papillary thyroid cancer (PTC) is the most common malignant tumor of the thyroid gland. It is highly malignant, mostly occurs in women, has a poor prognosis, and is very aggressive [1]. The invasiveness of PTC is related to the tumor's location, diameter, clinical stage, microcalcification, lymph node metastasis, lymph node dissection, and other factors [2]. The current assessment of PTC invasiveness is mainly based on histopathological findings. Histopathological manifestations are the most direct evidence of tumor invasiveness, but the subjectivity and uncertainty of pathological results make it difficult to evaluate the invasiveness of PTC [3]. Ultrasound imaging is a non-invasive examination method that can indirectly assess tumor invasiveness by evaluating tumor size,

shape, boundary, and other characteristics [4]. It can accurately diagnose PTC before surgery and has high application value in tumor diagnosis and evaluation. Serum indicators are important indicators for evaluating tumor invasiveness and prognosis, including serum thyroid stimulating hormone (TSH), thyroglobulin (Tg), thyroglobulin antibody (TgAb), and thyroid peroxide indicators such as thyroid peroxidase antibody (TPOAb) can be used as common indicators to predict the invasiveness of PTC. Still, their specificity and sensitivity are low [5,6]. Ultrasound imaging combined with serum indicators has high application value in assessing the invasiveness of PTC. This study intends to provide a basis for early prediction and prognosis of PTC invasiveness by analyzing the ultrasonic imaging characteristics of PTC and studying the correlation of serum indicators with the assessment of PTC invasiveness.

## 2. Materials and methods

### 2.1. General information

A total of 150 patients with PTC admitted to our hospital from September 2019 to December 2022 were selected, including 60 males and 90 females aged 25–81 years old, with an average age of 52.41 ± 6.77 years. All patients underwent pathological tissue examination and were divided into the PTC metastasis group ($n$ = 55) and PTC group ($n$ = 95) according to the size, shape, boundary, internal echo, and presence of microcalcification of the tumor. All patients were followed up to 12 months after surgery. Inclusion criteria: (1) Patients aged ≥ 18 years with PTC confirmed by postoperative pathology; (2) no prior history of radiotherapy, chemotherapy, or targeted therapy; (3) no contraindications to surgery. Exclusion criteria: (1) Patients younger than 18 years old or older than 70 years old; (2) patients with pathological diagnosis of non-papillary thyroid cancer; (3) patients who have received surgical treatment or chemotherapy; (3) patients with severe cardiovascular disease, liver, and kidney dysfunction; (4) patients who did not comply.

### 2.2. Method

Ultrasound imaging examination was carried out using a high-frequency ultrasonic diagnostic instrument with a probe frequency of 5–12 MHz. The patient was placed in a supine position with their neck fully exposed. First, a routine ultrasound scan was performed to observe the location, size, shape, boundary, internal echo, and other characteristics of the thyroid nodules. The blood flow signal inside the tumor was then observed and the blood flow grade was recorded.

Serum indicator was detected by extracting 5 mL of fasting venous blood from the patient, centrifuged to separate the serum, and stored in a -80°C refrigerator. The enzyme-linked immunosorbent assay (ELISA) was used to detect biochemical indicators related to tumor invasiveness in serum, such as tumor markers, growth factors, inflammatory factors, etc., and operated strictly with the kit's instructions.

### 2.3. Observation indicators

The detection rate of ultrasound imaging combined with serum indicators and the invasiveness of PTC were observed and analyzed (**Figure 1**).

### 2.4. Statistical methods

The SPSS 19.0 software was used to conduct a statistical analysis of the data of this study. Measurement data were expressed as mean ± standard deviation and the $t$-test was used for comparison between groups. Count data were expressed as %, and analyzed using the chi-squared ($\chi^2$) test. All measurement data followed a normal distribution and homogeneous variance. An independent sample $t$-test or rank sum test should be performed if the data is non-

normally distributed or has uneven variances. Results were considered statistically significant at $P < 0.05$.

# 3. Results

## 3.1. Comparison of detection rates between the two groups

As shown in **Table 1**, in the PTC group, the detection rates of ultrasound imaging, serum indicators, and ultrasound imaging combined with serum indicators were 91.58%, 90.53%, and 94%, respectively. In the PTC metastasis group, the detection rates of ultrasound imaging, serum indicators, and ultrasound imaging combined with serum indicators were 87.27%, 87.27%, and 90.91%, respectively. The detection rate of ultrasound imaging combined with serum indicators within the PTC group was significantly better than that of the PTC metastasis group ($P < 0.05$).

**Table 1.** Comparison of detection rates between the two groups [*n* (%)]

| Group | Ultrasound imaging | Serum indicators | Ultrasound imaging combined with serum indicators | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| PTC group ($n = 95$) | 87 (91.58) | 86 (90.53) | 94 (98.95) | 6.760 | < 0.05 |
| PTC metastasis group ($n = 55$) | 48 (87.27) | 48 (87.27) | 50 (90.91) | 0.476 | > 0.05 |
| $\chi^2$ | 0.718 | 0.387 | 3.955 | | |
| *P* | > 0.05 | > 0.05 | < 0.05 | | |

## 3.2. Comparison of serological characteristics between the two groups

As shown in **Table 2**, the levels of TSH, Tg, TgAb, and TPOAb of the PTC group were lower than those of the PTC metastasis group ($P < 0.05$).

**Figure 1** shows the automatic full-volume breast ultrasound scan of superficial small organs.

**Table 2.** Comparison of serological characteristics between the two groups (mean ± standard deviation)

| Group | TSH (mIU/L) | Tg (ng /L) | TgAb (IU/L) | TPOAb (IU/L) |
|---|---|---|---|---|
| PTC group ($n = 95$) | 3.26 ± 1.45 | 47.61 ± 7.36 | 5.16 ± 1.39 | 8.54 ± 2.14 |
| PTC metastasis group ($n = 55$) | 4.26 ± 1.45 | 52.26 ± 8.45 | 6.36 ± 2.14 | 10.41 ± 1.87 |
| *t* | 4.070 | 3.530 | 4.160 | 5.395 |
| *P* | < 0.05 | < 0.05 | < 0.05 | < 0.05 |

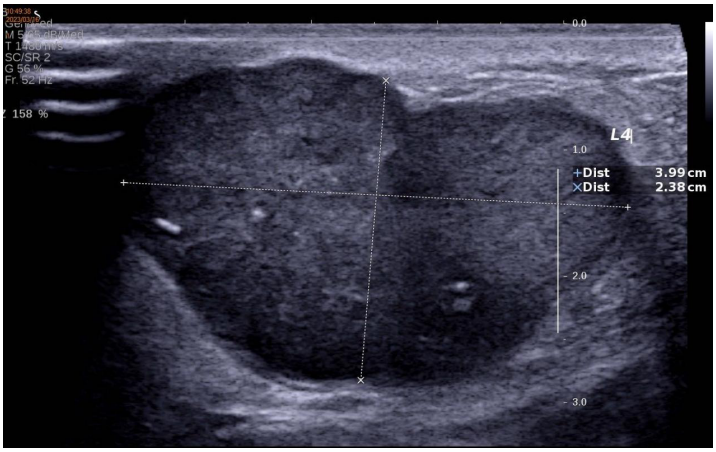


**Figure 1.** Automatic full-volume breast ultrasound scan of superficial small organs

## 4. Discussion

PTC is the most common clinical thyroid malignant tumor, accounting for approximately 80% of all thyroid cancers, the vast majority of which are papillary carcinomas. The invasiveness of thyroid cancer refers to the ability of tumor cells to break through the thyroid capsule and invade surrounding tissues, organs, and lymph nodes to cause metastasis [7]. Recently, the incidence of PTC has been increasing and tends to affect younger patients. The invasiveness of PTC is related to the size, shape, number, and blood supply of tumor cells. In clinical practice, the pathological diagnosis of PTC patients is mainly based on histopathological examination results [8]. However, due to the high degree of malignancy of PTC, its histopathological diagnosis is subjective and uncertain, and the pathological results are a dynamic process. Hence, it is difficult to accurately evaluate the invasiveness of PTC [9]. Ultrasound, a non-invasive examination method, has unique advantages in assessing tumor invasiveness. Due to its special histopathological characteristics, PTC is highly aggressive and highly invasive, prone to recurrence and metastasis, and has a poor prognosis. Therefore, early diagnosis, reasonable assessment of the invasiveness of PTC, and guidance of clinical treatment are important to improve the prognosis of PTC [10]. Recently, ultrasonic examination has become widely used in PTC. Ultrasound imaging and serum markers each play an important role in assessing the aggressiveness of PTC [11]. Ultrasound imaging can provide intuitive information about tumor shape, size, blood flow signals, etc. These characteristics are closely related to the biological behavior of tumors. Serum indicators, such as tumor markers, growth factors, and inflammatory factors, can reflect tumor activity, growth rate, and interaction with surrounding tissues [12].

In this study, the detection rates of ultrasound imaging, serum indicators, and ultrasound imaging combined with serum indicators of the PTC group were 91.58%, 90.53%, and 94%, respectively. In the PTC metastasis group, the detection rates of ultrasound imaging, serum indicators, and ultrasound imaging combined the detection rates of serum indicators were 87.27%, 87.27%, and 90.91%, respectively. The detection rate of ultrasound imaging combined with serum indicators within the PTC group was significantly better than that of the PTC metastasis group ($P < 0.05$). This indicates that ultrasonic imaging characteristics and serum indicators have a certain value in the invasiveness assessment of PTC, especially when used together. When used, the accuracy of prediction can be significantly improved, providing clinicians with a more reliable basis and helping formulate personalized treatment plans and predict patient prognosis. Combining ultrasound imaging with serum markers can more comprehensively assess the aggressiveness of PTC. Ultrasound imaging mainly focuses on observing the morphological structure and blood flow characteristics of tumors, while serum indicators reflect the biochemical characteristics of tumors. Combining the two can reveal the tumor's biological behavior and improve the accuracy of the assessment [13]. Through regular ultrasound imaging and serum index testing, the tumor's development trend and invasive changes can be observed, which is of great significance for formulating individualized treatment plans and predicting the prognosis of patients [14]. Ultrasound imaging examination and serum index detection are non-invasive, painless, radiation-free, and easily operable, making it convenient for repeated examinations and long-term follow-up [15].

The levels of TSH (mIU/L), Tg (ng/L), TgAb (IU/L), and TPOAb (IU/L) in the PTC group were 3.26 ± 1.45, 47.61 ± 7.36, 5.16 ± 1.39, and 8.54 ± 2.14, respectively. The levels of TSH (mIU/L), TG (ng/L), TGAb (IU/L), and TPOAb (IU/L) in the metastasis group were 4.26 ± 1.45, 52.26 ± 8.45, 6.36 ± 2.14, and 10.41 ± 1.87, respectively. The differences between the PTC and PTC metastasis groups were statistically significant ($P < 0.05$). There were significant differences in tumor markers among tumors with different degrees of invasiveness, which indicated that tumor markers may be related to the invasiveness of the tumors.

## 5. Conclusion

Ultrasound imaging combined with serum indicators demonstrated great promise in assessing the invasiveness of PTC but further research and improvement are still needed. Multidisciplinary cooperation and the introduction of advanced technology are expected to provide more accurate and personalized solutions for diagnosing and treating PTC. This study has some limitations. Firstly, a small sample size of only 150 patients was analyzed, and gender, age, clinical stage, or other factors were considered. Additionally, this study only analyzed the ultrasound imaging characteristics and serum indicators without conducting a correlation analysis with other indicators. To improve the accuracy in predicting the invasiveness of PTC, future research should conduct multi-center, large-sample studies.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Study on the Association of XRCC1 Gene rs72484243 Polymorphisms with Increased Laryngeal Cancer Risk

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**Abstract:** *Objective:* To study the association of X-ray repair cross-complementing group 1 (XRCC1) gene polymorphisms with increased laryngeal cancer risk. *Methods:* A total of 120 individuals, comprising 60 patients with laryngeal squamous cell carcinoma (LSCC), and 60 healthy volunteers participated were selected. Blood samples were taken and analyzed, and 4 XRCC1 polymorphisms (rs145135970, rs1799780, rs25489, and rs72484243) were genotyped. *Results:* Gender, age, body mass index (BMI), and smoking habits were shown to be the high-risk factors for LSCC. Genotype and allele distributions for the 4 polymorphisms differed significantly between both groups ($P < 0.05$). Furthermore, carriers with the rs72484243GTGT- allele exhibited an increased risk of LSCC relative to those who had the rs145135970 GTGTGTGTGTGTGT- allele, the rs1799780 G-A allele, or the rs25489 C-T allele, as determined by binary logistic regression analysis ($OR = 2.74$, 95% CI: 1.27–5.91, $P = 0.01$), after accounting for possible co-factors like sex, age, BMI, drinking and smoking behavior, and special diet requirements. In addition, a TA haplotype and a GTGTGTGTGTGTTG haplotype were linked to LSCC in Chinese populations in a haploid association study of 4 SNP loci in the XRCC1 gene ($P = 0.05$ $OR = 1.36$, 95% CI = 1.1228–1.6406). *Conclusion:* Genetic polymorphisms of the XRCC1 gene at the rs72484243 site were correlated with an elevated risk of LSCC among the Xinjiang population.

**Keywords:** XRCC1 gene; Single nucleotide polymorphism; Susceptibility gene; Laryngeal cancer

**Online publication:** March 29, 2024

## 1. Introduction

Head and neck squamous cell carcinomas (HNSCCs) is the sixth most prevalent types of malignancy worldwide and represent a heterogeneous group of malignancies that arise from the mucosal epithelium of the oral cavity, pharynx, nasal cavity, paranasal sinuses, and larynx [1,2]. Laryngeal squamous cell carcinoma (LSCC) accounts for one-third of all HNSCC cases and ranks second in terms of prevalence among cancers [3]. The incidence and mortality of laryngeal cancer worldwide were up to 2.76 cases/year per 100,000 population and 1.66 deaths/year per 100,000 population, respectively [4]. Men are predisposed to a greater risk of developing LSCC (5.8 cases per 100,000 for men vs 1.2 per 100,000 for women) [2].

The incidence varies considerably across different populations and ethnic groups [3,5,6]. This indicates that the risk of LSCC is influenced by various environmental and lifestyle factors. The human papillomavirus (HPV) and the Epstein-Barr virus (EBV) as well as occupational exposure to carcinogens are the most common causes of LSCC [6,7]. Due to the challenges in early diagnosis, three out of every five patients are already in an advanced state (stages III or IV) upon diagnosis [7]. Despite the overall decline in incidence over the last 4 decades, the 5-year survival rate has only dropped from 66% to 63%. Research should prioritize developing better methods of early detection as a means of increasing both the patient's survival rate and quality of life.

Laryngeal cancer has a complex etiology that includes exposure to common carcinogens, genetic polymorphism, HPV infection, immune suppression, laryngopharyngeal reflux, and occupational factors [8–10]. DNA damage could be induced by the aforementioned carcinogens, which may then trigger apoptosis or uncontrolled cell proliferation, eventually leading to cancer. Hence, DNA repair genes are crucial to ensure genomic integrity. This indicates that mutations in DNA-repair genes may contribute to the onset and progression of LSCC [11]. Studies showed that polymorphisms of GLUT1, HIF1α, and TBX21 genes had no association with laryngeal cancer development [12]. The telomerase reverse transcriptase gene TERT-CLPTM1L, plays a key role in the formation and progression of various cancers. Yu *et al*. reported that this gene may be a significant biomarker for the susceptibility to oropharyngeal and laryngeal cancers [13]. A study was carried out on the association between CD14 gene polymorphism and risk of laryngeal cancer [14]. Ekizoglu *et al*. indicated that the gene SLC22A23 (solute carrier family 22, member 23) may play a significant role in the risk of laryngeal cancer [15]. A recent study also showed that rs6620138DIAPH2 polymorphism could increase the onset risk of laryngeal cancer [16].

X-ray repair cross-complementing group 1 (XRCC1) is a gene that protects DNA against harmful carcinogens by participating in the base excision repair (BER) pathway. The XRCC1 protein is essential in the process of repairing single-stranded DNA fractures [11–17]. The protection is achieved based on the genes that are involved in DNA repair pathways and the maintenance of genomic stability [18–20]. Research has shown that various polymorphisms in DNA repair genes were linked to different pathologies, including lung cancer, polycystic ovary syndrome (PCOS), ovarian cancer, breast cancer, and myeloid leukemia [19,21–25]. Polymorphisms in DNA repair genes could influence the functioning of the protein products of those genes [19].

The three most crucial DNA repair pathways are BER, double-strand break (DSB) repair, and nucleotide excision repair (NER) [3]. The development of cancer begins with mutations and some studies suggested that impaired DNA repair was associated with a higher chance of developing several cancers [5–17]. Nonetheless, the XRCC1 gene's possible link to LSCC has only been the subject of a few studies [26]. Therefore, this study analyzes the association between polymorphisms in the XRCC1 gene and the risk of LSCC in a population from northwest China.

## 2. Methods

### 2.1. Ethical statement

This research was approved by the First Affiliated Hospital of Xinjiang Medical University ethics committee and it was conducted following the principles stipulated in the Helsinki Declaration. All participants or their legal guardians provided informed consent.

### 2.2. Subjects and clinical parameters

One hundred and twenty LSCC patients admitted between January 2021 to October 2023 were selected and divided into two groups, 60 patients with LSCC and 60 healthy individuals. The information on patients and control baseline characteristics (gender, age, drinking behavior, smoking status, and special diet requirements) was gathered via in-person interviews, health record searches, and pathology reports.

### 2.3. Blood sample preparation and DNA isolation

The patients were instructed to fast for more than 12 hours and blood was drawn from their cubital veins. Materials and reagents used include the whole blood genomics extraction kit (Tiangen Biochemical Technology Beijing Co., LTD), ABI 2720 Thermal Cycler (Applied Biosystems, Waltham, MA, USA), centrifuge model 581OR (Eppendorf (Hamburg, Germany)), XiangYi H1650-W (XiangYi, Hunan, China), the EP600 Gel electrophoresis meter (Shanghai Yubo Biotechnology Co., LTD.), the NanoDrop 2000 (NanoDrop Technologies, Wilmington, DE, USA), Invitrogen Qubit 3.0 Spectrophotometer (Invitrogen, Carlsbad, CA, USA), Illumina Hiseq/Nova seq (Illumina, CA, USA), the Agilent 2100 bioanalyzer (Agilent Technologies, USA), Herculase II Fusion DNA Polymerases (Agilent Technologies, CA, USA), TIANGEN Gel Extraction kit (TIANGEN, Beijing, China), 10X Reaction buffer and the Hot-start Taq polymerase (TaKaRa, Dalian, China).

### 2.4. Genotyping

The TM Multiple SNP Typing Kit (Shanghai Genesky Biotechnology) was used in this study for genotyping single nucleotide polymorphisms (SNPs). A ligase reaction with a high degree of specificity was utilized to identify the SNP allelic site. After that, the ligated products of different lengths were obtained by adding non-specific sequences of varying lengths at the end of the ligase probes, and a ligase addition reaction was performed. Following the amplification of the ligated products by PCR utilizing universal primers labeled with fluorescence, the products were separated by fluorescence capillary electrophoresis. Ultimately, the electrophoretic patterns were analyzed to determine the genotypes at each SNP locus.

### 2.5. Data analyses

The SPSS 26.0 software was utilized for analyses of statistical data. Measurement data were compared using the *t*-test and count data was analyzed using the chi-squared ($\chi^2$) test. The Wilcoxon Rank-Sum test was conducted to examine the BMI. The Hardy-Weinberg equilibrium (HWE) was assessed using the chi-squared test or SHEsis program. The genotypic and allelic association with the disease was analyzed utilizing the PLINK program [27]. The Haploview v4.2 (Broad Institute, Cambridge, MA, United States) was utilized to produce a linkage disequilibrium (LD) plot [28]. PLINK was utilized to analyze haplotype associations. To derive the odds ratios (ORs) and the 95% confidence intervals (CIs), logistic regression was utilized, with the adjustment of covariates. In addition, the SNPs were examined employing three different logistic regression models: recessive, dominant, and additive. All tests were two-tailed, and the results were considered statistically significant at $P < 0.05$.

# 3. Results

## 3.1. Baseline characteristics

**Table 1** illustrates the clinical features of the individuals who participated in this research. Among them, a comparison between gender, age, and smoking behavior showed statistical significance ($P < 0.05$). Hence, these factors were included in the subsequent logistic regression analysis as covariates. No statistical significance was found in the BMI, drinking, and special diet requirements between the LSCC patient group and the control group.

**Table 1.** Clinical characteristics of the collected LSCC population and controls

| Characteristic | LSCC ($n = 60$) | Control ($n = 60$) | *P* |
|---|---|---|---|
| Gender (M/F) | 56/4 | 30/30 | < 0.001 |
| Age, mean ± SD | 62.85 ± 8.93 | 53.67 ± 14.71 | < 0.001 |
| BMI, mean ± SD | 24.95 ± 3.57 | 25.88 ± 3.01 | 0.13 |
| Drinking | | | |
| No | 44 | 51 | 0.17 |
| Yes | 16 | 9 | |
| Smoking | | | |
| No | 20 | 45 | < 0.001 |
| Yes | 40 | 15 | |
| Special Diet Requirements | | | |
| No | 49 | 56 | 0.09 |
| Yes | 11 | 4 | |

## 3.2. Hardy–Weinberg (HWE) analysis of the examined SNPs

The results of the HWE analysis indicated that neither the LSCC patients nor the controls had any deviations from HWE for the three markers, rs145135970, rs1799780, and rs25489.

## 3.3. Genotypic and allelic correlation with LSCC

In the LSCC population, the allelic frequencies and genotypic distribution of the 4 variants (rs145135970, rs1799780, rs25489, and rs72484243) exhibited considerable variation between the LSCC and control group ($P < 0.05$). However, only the allelic frequencies of GTGT at the rs72484243 locus demonstrated a significant difference in allelic distribution ($P = 0.02$, 95% CI = 1.09–4.16). Patients who had the GTGT genotype had a risk of developing LSCC that was 2.13 times higher than the controls. After controlling for the effects of sex, age, and smoking habits, additional logistic regressions were performed using the recessive, dominant, and additive models. A strong link between the rs72484243 locus and the risk of LSCC was discovered under the additive and dominant models. The GTGT allele was associated with a 2.74-fold higher risk of LSCC. These data are summarized in **Table 2** and **Table 3.**

The Manhanttan plot of the chi-squared allelic test is illustrated in **Figure 1**.

**Table 2.** Allelic association analysis between four SNPs and LSCC

| SNP | Ref | Alt | Model | LSCC (11\|10\|00) | Control (11\|10\|00) | $\chi^2$ | OR (95%CI) | *P* |
|---|---|---|---|---|---|---|---|---|
| rs145135970 | GTGTGTGT | - | Allele | 5/115 | 13/103 | 4.15 | 0.34 (0.12–0.99) | 0.04 |
| rs1799780 | G | A | Allele | 5/115 | 15/101 | 5.84 | 0.29 (0.1–0.83) | 0.02 |
| rs25489 | C | T | Allele | 5/115 | 15/103 | 5.64 | 0.29 (0.1–0.85) | 0.02 |
| rs72484243 | GTGT | - | Allele | 31/89 | 16/98 | 5.07 | 2.13 (1.09–4.16) | 0.02 |

Abbreviation: Reference allele, ref; altered allele, alt; number of homozygous mutations, heterozygous mutations, and homozygous normal in the sample, 11|10|00; the t-statistic of the coefficient, STAT.

**Table 3.** Logistic regression analysis of XRCC1 polymorphisms and risk of LSCC in our cohort

| SNP | Allele | Model | OR (95%CI) | *P* |
|---|---|---|---|---|
| rs145135970 | GTGTGT- | Additive model | 0.31 (0.1–0.95) | 0.04 |
| | | Dominant model | 0.31 (0.1–0.95) | 0.04 |
| | | Recessive model | NA | NA |
| rs1799780 | G-A | Additive model | 0.32 (0.11–0.91) | 0.03 |
| | | Dominant model | 0.31 (0.1–0.95) | 0.04 |
| | | Recessive model | NA | NA |
| rs25489 | C-T | Additive model | 0.33 (0.12–0.92) | 0.03 |
| | | Dominant model | 0.32 (0.11–0.97) | 0.04 |
| | | Recessive model | NA | NA |
| rs72484243 | GTGT- | Additive model | 2.74 (1.27–5.91) | 0.01 |
| | | Dominant model | 2.74 (1.27–5.91) | 0.01 |
| | | Recessive model | NA | NA |

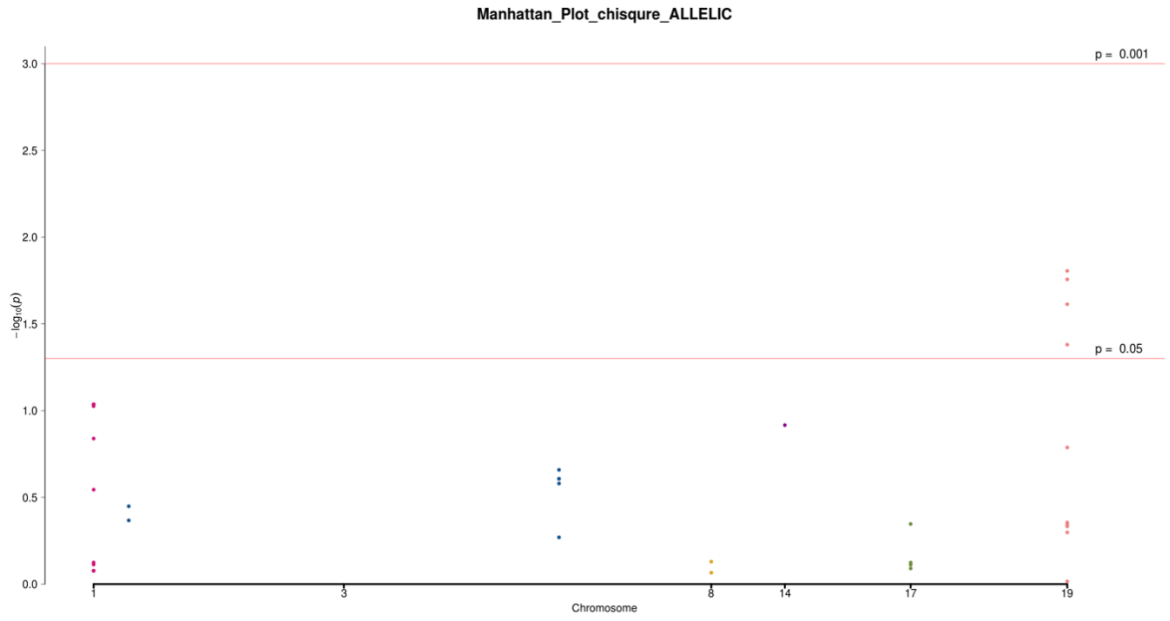


**Figure 1.** Manhattan plot of chi-squared allelic test

### 3.4 Haplotypes associated with LSCC

LD analysis indicated strong associations between rs25489 and rs1799780 with LSCC, where D' = 1, the logarithm of the odds (LOD) = 24.93, $r^2$ = 1, and Dist = 864 (**Table 4**). Three XRCC1 SNP loci were analyzed for haploid frequency, revealing four haplotypes at the three loci. However, the difference in the distribution of haplotypes GTGTGTGTGTGTGTCG and GTGTGTGTGTGTGTCA in the LSCC population was not statistically significant ($P > 0.05$). Conversely, the distribution of haplotypes-TA and GTGTGTGTGTGTGTTG were significantly different between both groups ($P < 0.05$). The risk of developing LSCC increased by 0.12 and 0.35 for the -TA and GTGTGTGTGTGTGTTG haplotype carriers respectively, as shown in **Table 5**.

The LD for the three SNPs that were studied in LSCC populations is depicted in **Figure B**.

**Table 4.** Association between SNPs with LSCC

| SNPs | D' (95%CI) | LOD | $r^2$ | Dist |
|---|---|---|---|---|
| rs145135970\|rs25489 | 1 (0.87–1) | 19.99 | 0.89 | 8918 |
| rs145135970\|rs1799780 | 1 (0.87–1) | 19.92 | 0.89 | 9782 |
| rs25489\|rs1799780 | 1 (0.92–1) | 24.93 | 1 | 864 |

Abbreviation: Linkage disequilibrium, LD; the value of D' (0~1) between the two loci, D', D'=D/Dmax; the log of the likelihood odds ratio, a measure of confidence in the value of D', LOD; the correlation coefficient between the two loci, $r^2$; the distance before the two SNPs, dist.

**Table 5.** Association of haplotypes with LSCC (logistic regression).

| Haplotype | LSCC | Control | Estimate | SE | P-value | OR (95%CI) | SNPs |
|---|---|---|---|---|---|---|---|
| -TA | 8 (6.67%) | 19 (15.83%) | 1.53 | 0.51 | 0.03 | 0.12 (0.01–1.07) | rs145135970\|rs25489\|rs1799780 |
| GTGTCG | 14 (11.67%) | 18 (15.25%) | 0.006 | 0.19 | 0.82 | 0.53 (0.37–1.62) | rs145135970\|rs25489\|rs1799780 |
| GTGTTG | 23 (19.17%) | 11 (9.17%) | 1.21 | 0.64 | 0.04 | 0.35 (0.01–1.21) | rs145135970\|rs25489\|rs1799780 |
| GTGTCA | 13 (10.83%) | 17 (14.17%) | 0.05 | 0.24 | 0.32 | 0.28 (0.01–0.6) | rs145135970\|rs25489\|rs1799780 |

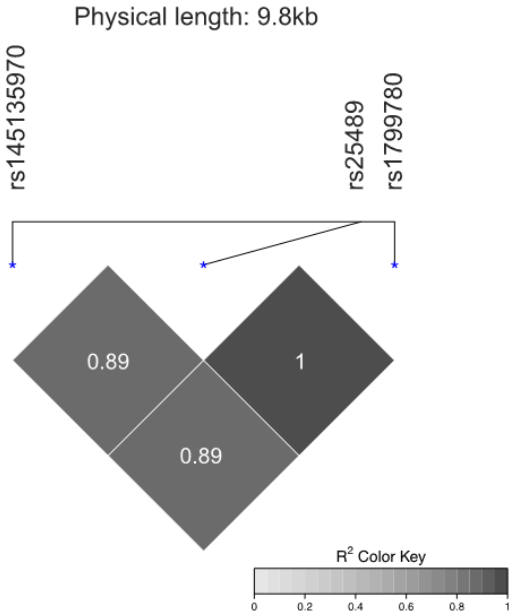


**Figure 2.** Depiction of LD for the three SNPs studied in LSCC populations

## 4. Discussion

This study demonstrated that the rs72484243 gene variants were linked to an increased LSCC risk in the population from northwest China. According to our knowledge, this is the first study that describes the link between the gene rs72484243 and the risk of LSCC.

As the most prevalent tumor of the upper respiratory tract, laryngeal cancer is a global health problem with a dismal prognosis and a high recurrence rate [29]. It is a set of head and neck cancers (HNC) that accounts for around 20% of all cancer cases. Unfortunately, laryngeal cancer is generally detected after it has already advanced to late stages [30]. Causes of laryngeal cancer primarily include smoking, alcohol consumption, HPV infection, and genetic predisposition [31–33]. In addition, having a family history of kidney and colorectal cancer was also associated with a greater risk of developing laryngeal cancer [34]. Numerous studies provided evidence that certain heritable factors have a role in the onset and progression of laryngeal cancer, including cyclin-dependent kinase, DNA repair gene, NER pathway gene, special AT-rich sequence-binding protein 1 and 2, B-cell translocation gene 1, matrix metalloproteinase 11, P14, epidermal growth factor-like domain 7 (Egfl7), and methylene tetrahydrofolate reductase [35–41].

There is a significant difference in LSCC survival rates based on factors like sex, age, stage of malignancy, and therapy measures [42–45]. The 5-year survival rate is > 90 % for patients who are in stages I or II, but is <60 % for patients who are in a locoregional advanced stage [46]. Researchers have discovered several genes involved in the DNA repair pathways for their potential involvement in the onset and progression of laryngeal cancer. Nevertheless, the findings were not conclusive. Therefore, patients with LSCC might benefit from the discovery of novel tumor biological markers that may aid in early diagnosis and therapy choices [47].

DNA repair is an essential mechanism in the protection of cells against carcinogenesis. Genomic instability may be triggered by environmental carcinogen-caused DNA damage. Therefore, alterations in DNA repair genes may affect an individual's susceptibility to cancer, as well as their therapeutic response and prognosis. The link between polymorphisms in the *XRCC1* gene Arg399Gln, *XRCC3* gene Thr241Met, and XPD was discovered through a meta-analysis. According to recent findings, DNA damage, which may be triggered by exposure to UV light, ionizing radiation, or environmental chemicals, is possibly the most critical factor that causes human malignancies [48]. The cell is stimulated to initiate the process of DNA repair when it experiences DNA damage. DNA repair systems are critical to maintaining genomic stability and are significantly involved in the prevention of mutations.

XRCC1 is a common DNA repair gene found on chromosome 19q13.2–13.3 that primarily functions in the process of DNA BER [49,50]. It is responsible for the formation of enzyme complexes that are optimized for the repair of single-strand breaks. In addition, it is also involved in other repair pathways by recruiting and organizing a vast number of enzymes in multi-step repair processes [51]. One of the XRCC1 polymorphisms, Arg399Gln (G to A; rs25487) on exon 10, has been linked to DNA repair impairment and high DNA adducts by altering XRCC1 protein functions [52]. The XRCC1 gene has also been linked to many different types of cancer, as well as diabetes and coronary artery disease [53–55]. Additionally, Arg399Gln XRCC1 is critical in the onset and progression of cervical cancer and endometriosis [50–56]. According to a previous study, SNPs in the coding region can affect DNA repair ability and are closely linked to the genetic susceptibility of many tumors, including HNC [57]. Amino acid substitution attributable to SNPs occurs most frequently at exonsArg194Trp, Arg280His, and Arg399Gln [58–60]. Protein-protein interactions involving XRCC1 and other BER proteins could be affected as a result of the amino acid alterations, which might alter DNA repair capabilities [58]. Previous studies have focused on the XRCC1 Arg399Gln SNP gene because of its association with an elevated risk of many malignancies, including HNC [61,62]. According to Wang *et al*., Arg399Gln variants of XRCC1 were linked

to a greater risk of HNSCC in Caucasians, as well as an enhanced risk of LSCC [60]. Conversely, Wu illustrated that polymorphism of XRCC1 Arg399Gln was not linked to an elevated risk of HNC [60]. XRCC-1 polymorphic hetero genotype (CT) and mutant genotype (TT) variants have been proven to be risk factors in loco-regionally progressed LSCC [63]. One meta-analysis that included 14586 participants showed that XRCC1 Arg399Gln variants (Arg/Gln and Arg/Arg+Arg/Gln) may increase the risk of HNC Caucasians [64].

We identified significant variations between LSCC and control groups in the genotypic and allelic frequencies of the rs72484243 locus. We discovered that the GTGT-genotype and the allele at the rs72484243 site of the XRCC1 gene were linked to the risk of LSCC in the population of Xinjiang China, which could be useful information for future clinical diagnosis and therapy. This study has some limitations. First, since only 60 people with LSCC in northwest China were included in this study, the findings may not be generalizable to the rest of the country and globally. Nevertheless, our findings provide a solid groundwork for future large-scale investigations. Secondly, this study only examined the polymorphism of the associated genes in LSCC patients, but not its role in the development of LSCC. Lastly, the candidate gene was selected based on the findings of relevant literature. Hence, validation is essential in future research.

## 5. Conclusion

Genetic polymorphisms of the XRCC1 gene at the rs72484243 site were associated with an elevated risk of LSCC among the Xinjiang population.


## Funding

Natural Science Foundation of Xinjiang Uygur Autonomous Region (Grant Number: 2021D01C320).


## Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Comparative Efficacy of Whole-Brain Radiotherapy Combined with Supplemental Precision Radiotherapy and Whole-Brain Radiotherapy Alone for Brain Metastases

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**Abstract:** *Objective:* To investigate the efficacy of whole-brain radiotherapy combined with supplemental precision radiotherapy compared to whole-brain radiotherapy alone for brain metastasis. *Methods:* Twenty-six cases of patients with brain metastasis were observed from January 2020 to June 2023. Thirteen cases each were randomly assigned to the observation group and the control group. The patients in the observation group received whole-brain radiotherapy combined with supplemental precision radiotherapy, while those in the control group received only whole-brain radiotherapy. *Results:* Comparing the quality of life scores between the two groups, the data from the observation group was significantly superior ($P < 0.05$). The survival rate of the observation group was higher than that of the control group, and their survival time was longer ($P < 0.05$). Additionally, compared with the control group, the observation group exhibited lower levels of various serum tumor factors after treatment ($P < 0.05$). *Conclusion:* Whole-brain radiotherapy combined with supplemental precision radiotherapy demonstrates improved clinical efficacy, prolonged survival time, and enhanced quality of life for patients with brain metastasis. These findings warrant further study and promotion.

**Keywords:** Brain metastasis; Whole-brain radiotherapy; Supplemental precision radiotherapy; Therapeutic efficacy

**Online publication:** March 29, 2024

## 1. Introduction

Brain metastasis occurs in approximately 30% of all cancers, with lung cancer being particularly prevalent, accounting for up to 80%. When brain metastasis develops in lung cancer patients, it not only diminishes their quality of life (QoL) but also shortens their survival time, thereby adversely affecting their prognosis. Currently, whole-brain radiotherapy (WBRT) is the primary treatment modality for brain metastasis in lung cancer patients. It aims to eradicate metastatic cancer cells using radiation, alleviate clinical symptoms, and enhance survival rates, thus becoming the preferred treatment option [1].

However, studies have indicated that WBRT often leads to adverse side effects and fails to achieve

satisfactory therapeutic outcomes. Supplemental precision radiotherapy, on the other hand, targets lesions with precision, thereby enhancing treatment accuracy and improving patients' quality of survival. By combining these modalities, a synergistic effect can be achieved, leading to improved patient outcomes [2,3]. This paper aims to investigate the efficacy of WBRT combined with supplemental precision radiotherapy.

## 2. Materials and methods

### 2.1. General information

The primary cases in this study were patients diagnosed with brain metastasis between January 2020 and June 2023), divided into 2 groups, each comprising 13 cases.

Inclusion criteria: (1) Diagnosis of brain metastasis confirmed by imaging with a measurable or evaluable intracranial lesion [4]; (2) Informed consent obtained from patients and their families; (3) No history of previous radiotherapy treatments.

Exclusion criteria: (1) Presence of cerebral infarction or other severe brain diseases; (2) Existence of drug contraindications; (3) Presence of comorbid mental health disorders.

In the observation group of 13 cases, there were 8 males and 5 females, with an average age of 68.25 ± 2.41 years, ranging from 52 to 84 years. The duration of illness ranged from 1 to 4 years, with an average of 2.51 ± 0.32 years. Pathological types included squamous carcinoma (5 cases), adenocarcinoma (5 cases), and adenosquamous carcinoma (3 cases). ECOG scores ranged from 0 to 2 points, with an average of 1.13 ± 0.03. In the control group of 13 cases, there were 9 males and 4 females, with an average age of 68.25 ± 2.41 years, ranging from 53 to 84 years. The duration of illness ranged from 2 to 4 years, with an average of 2.99 ± 0.41 years. Pathologic types included squamous carcinoma (4 cases), adenocarcinoma (8 cases), and adenosquamous carcinoma (1 case). ECOG scores ranged from 1 to 2 points, with an average of 1.58 ± 0.05 points. Comparison of the aforementioned indicators (age, gender, disease duration, pathologic type, and ECOG score) showed no significant differences ($P > 0.05$), allowing for valid comparisons.

### 2.2. Methods

Prior to radiotherapy implementation, both groups underwent magnetic resonance imaging (MRI) and computed tomography (CT) examinations to determine the initial lesion state. The control group received standard WBRT (irradiation of the patient's entire brain), delivering a dose of 30 Gy per day, five times a week. The observation group received supplemental precision radiotherapy in addition to standard WBRT. This involved targeting the lesion directly and interpolating distant tumors, utilizing gyro-rotating cobalt-60 stereotactic radiation technology. Approximately 80%–90% of the isodose curve covered the tumor edge, with a total dose ranging from 16 to 30 Gy, a single dose of 10 to 12 Gy, and an average target area dose of 17.1 Gy (ranging from 10 to 30 Gy).

### 2.3. Observation indexes

Various parameters were assessed for comparison between the two groups after treatment, including QoL scores, adverse reactions, survival time and rate, and serum tumor factors.

The SF-36 scale was employed to evaluate patient QoL, comprising four items, with scores indicating a positive correlation with patient QoL [5].

The ELISA method was utilized to analyze serum tumor factors in both groups, with pre-treatment and post-treatment serving as the observation points. Three milliliters of venous blood were collected from fasting patients in the early morning, placed in Eppendorf tubes, centrifuged at 2000 revolutions per minute for 5

minutes, and then stored at -80°C until examination.

### 2.4. Statistical analysis

Data analysis was conducted using SPSS 20.0, employing statistical methods appropriate for the dataset. All measurement data followed a normal distribution and were expressed as mean ± standard deviation (SD), with *t*-tests performed accordingly. Count data were expressed as *n* (%), with $\chi^2$ tests applied. A significance level of $P < 0.05$ indicated statistical significance.

## 3. Results

### 3.1. Comparison of quality of life scores between the two groups

**Table 1** shows that the observation group had higher QoL scores as compared to the control group ($P < 0.05$).

**Table 1.** Comparison of quality of life scores (mean ± SD, points)

| Group | *n* | Environment | Physical health | Social relationships | Psychological health |
|---|---|---|---|---|---|
| Observation group | 13 | 49.63 ± 2.11 | 58.96 ± 2.41 | 77.85 ± 3.45 | 13.85 ± 1.17 |
| Control group | 13 | 34.52 ± 2.01 | 44.25 ± 1.09 | 63.21 ± 2.08 | 5.22 ± 1.06 |
| *t* | - | 18.695 | 20.052 | 13.103 | 19.709 |
| *P* | - | 0.000 | 0.000 | 0.000 | 0.000 |

### 3.2. Comparison of adverse reactions between the two groups

There were no significant differences in adverse reactions for both groups ($P > 0.05$), as shown in **Table 2**.

**Table 2.** Comparison of the incidence of adverse reactions in the two groups

| Group | *n* | Gastrointestinal reactions (*n*) | Bone marrow suppression (*n*) | Liver impairment (*n*) | Total [*n* (%)] |
|---|---|---|---|---|---|
| Observation group | 13 | 1 | 0 | 0 | 1 (7.79) |
| Control group | 13 | 1 | 0 | 1 | 2 (15.38) |
| $\chi^2$ | - | | | | 0.377 |
| *P* | - | | | | 0.539 |

### 3.3. Comparison of survival time and rate

**Table 3** shows that the survival rate of the observation group was significantly higher than that of the control group, and the survival time was significantly longer as compared to the control group ($P < 0.05$).

**Table 3.** Comparing the survival time and rate of the two groups

| Group | *n* | Overall survival rate [*n* (%)] | PFS time (mean ± SD, months) |
|---|---|---|---|
| Observation group | 13 | 12 (92.31) | 26.58 ± 2.11 |
| Control group | 13 | 3 (23.08) | 5.63 ± 1.02 |
| $t$ / $\chi^2$ | - | 12.764 | 32.231 |
| *P* | - | 0.000 | 0.000 |

### 3.4. Comparison of serum tumor factor levels between the two groups

After treatment, the observation group had significantly lower levels of various serum tumor factors as compared to the control group ($P < 0.05$), as shown in **Table 4**.

**Table 4.** Comparison of serum tumor factor levels before and after treatment (mean ± SD)

| Group | TNF-α (pg/mL) | | NSE (ng/mL) | | SCC Ag (ng/mL) | | CEA (ng/mL) | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Observation group ($n$ = 13) | 26.58 ± 2.01 | 17.25 ± 1.02* | 25.85 ± 1.46 | 7.22 ± 1.01* | 24.77 ± 1.63 | 11.02 ± 1.45* | 97.85 ± 2.41 | 43.55 ± 2.32* |
| Control group ($n$ = 13) | 26.55 ± 2.02 | 21.66 ± 1.36* | 25.86 ± 1.47 | 12.85 ± 1.79* | 24.78 ± 1.65 | 18.52 ± 1.09* | 97.86 ± 2.40 | 84.85 ± 5.49* |
| $t$ | 0.038 | 9.353 | 0.017 | 9.877 | 0.016 | 14.907 | 0.011 | 24.984 |
| P | 0.970 | 0.000 | 0.986 | 0.000 | 0.988 | 0.000 | 0.992 | 0.000 |

* $P < 0.05$ compared to pre-treatment.

## 4. Discussion

With the continuous advancement of medical research and the enhancement of medical capabilities, the cure rates for malignant tumors have significantly improved. Among these, brain metastasis from lung cancer, characterized by its challenging treatment and poor prognosis, saw a turning point in the mid-1970s with the gradual inclusion of radiotherapy in its treatment regimen, leading to a significant increase in patient survival rates [6]. The scope of intracranial tumor radiotherapy applications primarily includes incompletely resected tumors, tumors spreading within the central nervous system, and preventing tumor recurrence post-resection. However, these treatments are contraindicated for children under three years of age. In cases where children cannot tolerate radiotherapy, chemotherapy may be administered to manage the condition [7].

In this study, the observation group exhibited superior survival times and rates compared to the control group, along with higher QoL scores. This suggests that combined treatment prolongs patient survival, positively impacting therapeutic outcomes and enhancing patient QoL. Research indicates that WBRT can eliminate microscopic foci and residual cancer cells, thereby extending patient survival. However, traditional radiotherapy often necessitates high drug doses, leading to various irreversible neurotoxicities such as dementia and cerebral necrosis [8]. Modern selective WBRT, facilitated by MRI, offers an alternative. Supplemental precision radiotherapy, employing advanced techniques like three-dimensional treatment planning, multi-leaf grating, and CT simulation positioning, enhances treatment efficacy while safeguarding normal brain tissue. The synergistic effect of combining these modalities surpasses that of WBRT alone, improving patient prognosis [9].

Comparing tumor factor levels between the two groups post-treatment, the observation group exhibited lower serum tumor factor levels, suggesting that combined treatment enhances patient immune function, thereby preventing disease deterioration. Tumor necrosis factor-alpha (TNF-α), a pro-inflammatory factor, is implicated in immune and inflammatory responses, particularly in malignant tumors, where elevated levels promote cancer cell growth and metastasis. Neuron-specific enolase (NSE), abundant in human nerve cells, aids in disease recurrence prediction, while squamous cell carcinoma antigen (SCC Ag) and carcinoembryonic antigen (CEA) serve as specific markers for squamous cell carcinoma (SCC) and various tumors, respectively. Monitoring these indices enables timely assessment of patient condition changes and treatment efficacy. Brain metastasis typically spreads via the bloodstream, detectable through imaging examinations. However, due to subclinical lesions, WBRT remains the primary treatment modality [10]. Despite extending survival, high-dose

radiotherapy may induce radiation encephalopathy, with doses generally limited to 30–40 Gy. Consequently, clinical efficacy may be compromised, with some patients experiencing recurrence or inadequate tumor control. Precision radiotherapy, a newer modality, ensures accurate patient positioning and preserves QoL [11].

Although controversial, some scholars advocate for combining WBRT with supplemental precision radiotherapy to enhance patient prognosis and reduce toxicity. This study aligns with this perspective. However, uncertainties remain regarding the selection criteria for different chemotherapeutic regimens. Moreover, this study's small sample size and short duration introduce bias in treatment selection and outcomes assessment, limiting its generalizability. Therefore, future studies should expand sample sizes and extend study durations to validate the efficacy of WBRT combined with supplemental precision radiotherapy.

In conclusion, compared to WBRT alone, the combination of WBRT and supplemental precision radiotherapy yields significantly improved efficacy, increasing patient survival rates and enhancing QoL. This warrants further investigation and promotion.

## Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Analysis of a Case of Airway Hemangioma in a 1-Month-Old Infant with Dyspnea – A Secondary Publication

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**Abstract:** Infantile hemangiomas are the most common benign tumors of infancy. However, hemangiomas located in the respiratory tract are rare and could cause life-threatening events due to airway obstruction. To date, the best recommended treatment for infantile hemangioma is oral propranolol as it exhibits faster effects with fewer adverse effects as compared to systemic corticosteroid therapy. In this study, we reported a case of a 1-month-old girl who was presented with respiratory symptoms and hemangioma on the scalp. The hemangioma extended from the right base of the skull to the thoracic inlet, causing inspiratory stridor and dyspnea. Treatment with oral propranolol was initiated and her symptoms regressed. Imaging showed regression of the hemangioma. This was a rare case of skin hemangioma found on the scalp, in which the hemangioma extended from the base of the skull to the subglottis, precipitating respiratory symptoms from airway obstruction. Based on this encounter, the presentation of skin hemangioma on the head, coupled with respiratory symptoms, necessitates the use of imaging studies, such as computed tomography, ultrasound, and magnetic resonance imaging to ascertain the extent of hemangioma.

**Keywords:** Infant; Hemangioma; Airway; Propranolol

**Online publication:** March 29, 2024

## 1. Introduction

Infantile hemangiomas are the most common benign tumors of childhood, occurring in 3%–10% of children, with a female-to-male ratio of 3:1 [1]. More than 60% of infantile hemangiomas occur in the skin of the face, head, and neck region, while endotracheal and subglottic hemangiomas are rare, accounting for approximately 1.5% of congenital laryngeal malformations [2,3].

Subglottic hemangiomas rarely cause stridor on inhalation and are typically present in the first few months of life, with 85% of cases occurring around 6 months of age, with a male-to-female ratio of 1:2. Other comorbidities include stridor, stridor cough, cyanosis, dysphagia, hemoptysis, and growth retardation. Only 1%–2% of patients with cutaneous hemangiomas have subglottic hemangiomas. However, there were reports of cutaneous lesions in 50% of patients with subglottic hemangiomas [4]. Corticosteroids and interferon-α have

been used to treat infantile hemangiomas in the past, but propranolol is currently the first-line treatment for infantile hemangiomas [5]. In this study, a case of a 1-month-old infant who was presented with respiratory distress, diagnosed with an upper airway hemangioma, and was treated with oral propranolol was reported. This resulted in lesion regression and symptomatic improvement.

## 2. Case description

A 1-month-old girl diagnosed with dyspnea and stridor on exhalation was the subject of this study. TThe patient was healthy after birth, but at 3 weeks of age, she developed dyspnea and stridor on inhalation and was hospitalized at a secondary hospital for treatment. She was transferred to our hospital because her symptoms did not improve. The patient reported that her breathing was not disturbed when feeding but became more difficult. Her breathing sound was also reduced when sleeping in the prone position. At the time of hospitalization at another hospital, there were no symptoms of hypoxia or apnea. However, antibiotic treatment did not alleviate the symptoms. There were no other symptoms such as coughing. Regarding the patient's past medical history, she was born at 40 weeks gestational age, with a 3,200 g birth weight. It was a spontaneous delivery and the patient had no unusual medical history other than receiving phototherapy for hyperbilirubinemia on the 6$^{th}$ day of life. The patient's family had no history of respiratory disease. Upon physical examination, it was found that the patient was 54.4 cm tall (10–25th percentile) and weighed 4.2 kg (3–5th percentile). On presentation, blood pressure was determined to be 80/50 mmHg, respiratory rate of 48 breaths/min, heart rate of 150 beats/min, body temperature of 36.6°C, and an oxygen saturation of 100% on room air. Stridor was auscultated on inspiration and retraction of the upper abdominal bones was observed on breathing, but there was no cyanosis or apnea, and no wheezing or bullae were heard during auscultation.

The patient had a 15 mm × 20 mm hemangioma with indistinct borders in the right parietal scalp area (**Figure 1**).

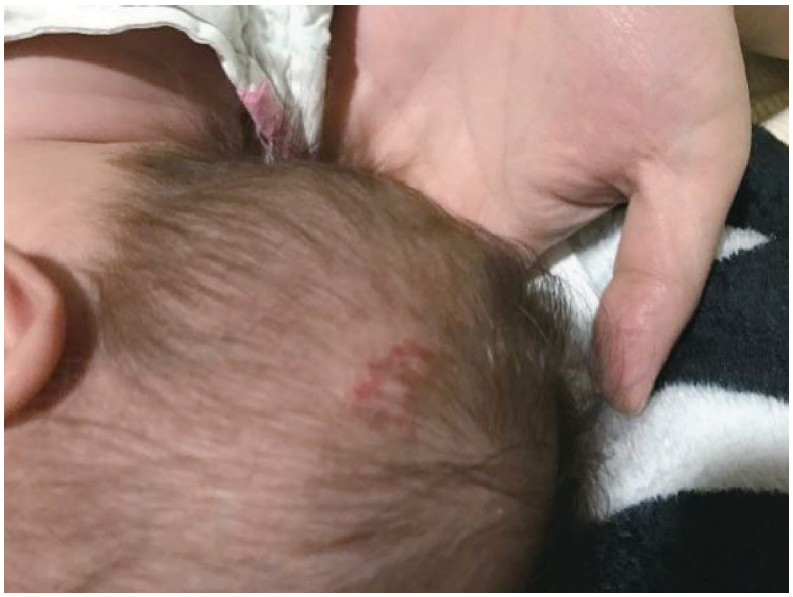

**Figure 1.** Hemangioma on the right parietal scalp

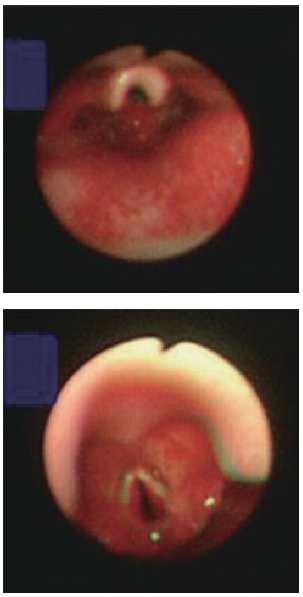

**Figure 2.** Initial findings of flexible bronchoscopy (A, B) show extended pink to red color mucosa with swelling of the posterior pharyngeal wall, vestibular folds, arytenoid cartilage, and vocal cord.

The chest radiograph and blood tests were unremarkable. Flexible bronchoscopy was performed, which revealed edema and redness of the vocal cords, pseudovocal cords, and subcondylar cartilage (**Figure. 2**). Nasopharyngeal aspirate specimens from other hospitalizations were tested for 14 respiratory viruses, all of which were negative. Neck cervical spine (AP) and lateral view via simple radiographs were unremarkable.

## 3. Treatment and patient outcome

The patient was diagnosed with laryngomalacia exacerbated by edema of the vocal cords and surrounding area due to an upper respiratory tract infection (URTI) of unknown etiology by bronchoscopy and was treated with intravenous cefotaxime (50 mg/kg, 3 times/day) and dexamethasone (0.3 mg/kg, total dose), with subsequent symptom improvements. Flexible bronchoscopy was repeated on the 4th day of hospitalization and showed significant improvement in the previous findings. The patient was discharged with the decision to follow up in the outpatient department.

Two days after discharge, the patient was readmitted to the hospital due to dyspnea. At the time of readmission, the patient's oxygen saturation dropped to 92%–93% in room air, so she was treated with a nasal cannula of 1 L/min oxygen. Due to similar symptoms as the previous hospitalization, she was suspected to have laryngomalacia with the same infection as before. The patient was treated with intravenous dexamethasone (0.6 mg/kg/day for a total of 3 doses) and inhaled steroids. However, her symptoms improved and then worsened again.

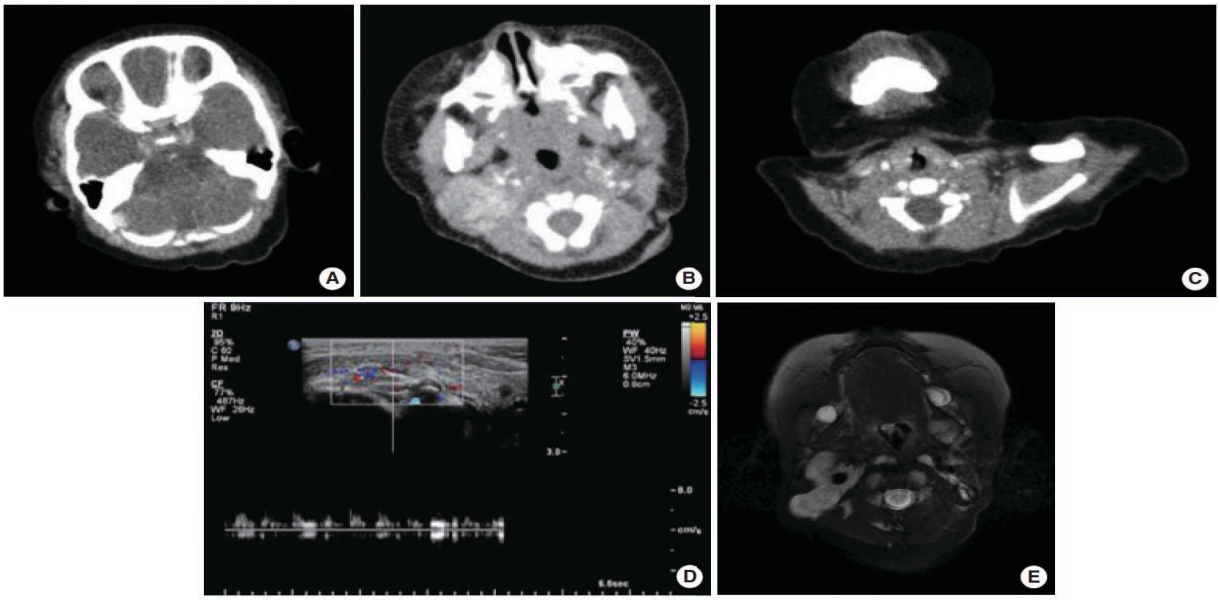


**Figure 3.** (A) Computed tomography (CT) image shows diffuse ill-defined, well-enhancing mass-like lesion at the parietal area. Panels B and C are continuous CT images, lesion was seen to extend to the thoracic inlet, causing a mass effect on the airway. (D) Soft tissue ultrasonography shows a hypoechoic mass-like lesion with prominent internal vascularity (venous flow noted) in the right posterior neck muscular layer which was posterior to the parotid gland. (E) Magnetic resonance image (MRI) shows a T2-weighted image high signal lesion in the right posterior neck area, including a right carotid space and posterior cervical space.

To differentiate the cause, a CT scan of the head and upper chest was performed. This showed a contrast-enhancing lesion with indistinct borders extending to the muscular layer from the right skull base to the thoracic inlet, suggesting a vascular malformation (**Figure. 3A, 3B, 3C**). It was hypothesized that the hemangioma observed in the right parietal scalp extended to the upper airway, causing airway edema. Ultrasonography

confirmed venous flow to the area of the hypoechoic mass from the right posterior neck muscle layer to the parotid gland (**Figure. 3D**), and magnetic resonance imaging (MRI) confirmed a hyperintense lesion on T2 weighted image (T2WI) in the right posterior neck region, including the right carotid artery region and posterior neck space, leading to the final diagnosis of hemangioma (**Figure. 3E**).

It was speculated that the patient's primary lesion, the upper airway, had fewer beta receptors, hence treatment with beta-blocker propranolol would be less effective. However, due to the recurrent dyspnea and the possibility that the lesion could develop into an airway obstruction, which requires tracheostomy and mechanical ventilation if it continues to increase in size, oral treatment with propranolol (0.5 mg/kg/day) with electrocardiogram (ECG) monitoring was initiated after full consultation with the guardian. On day 2, the patient did not develop dyspnea without intravenous dexamethasone or inhaled steroids and had no stridor on exhalation. The dose was increased to 1 mg/kg/day on day 3 and increased to 2 mg/kg/day on day 7, and no adverse events were observed.

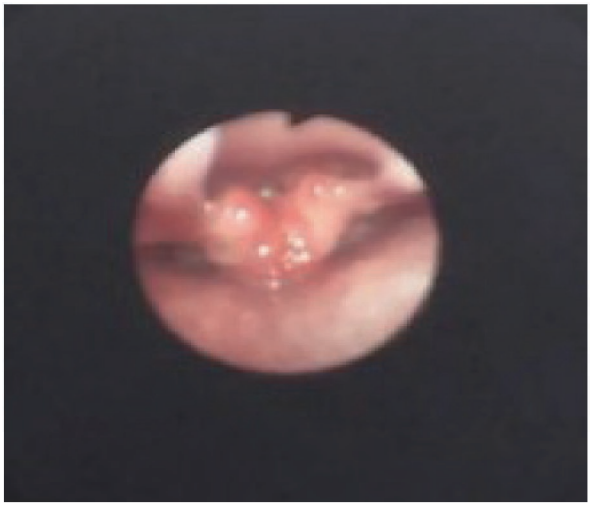

**Figure 4.** Follow-up bronchoscopy shows regression of hemangioma on the 7$^{th}$ day of treatment

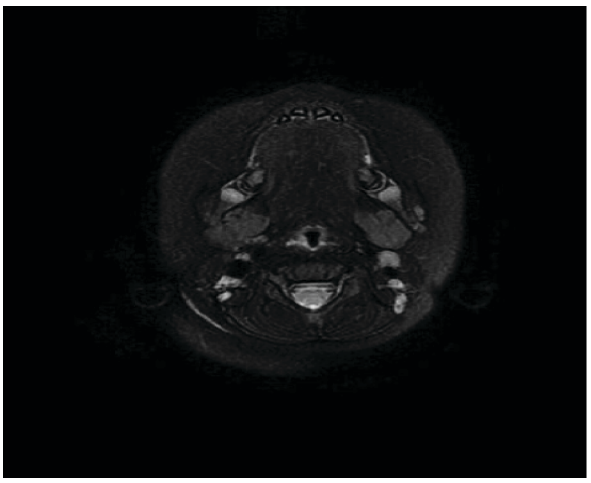

**Figure 5.** Brain MRI after 1 year of treatment shows regression of hemangioma

A follow-up bronchoscopy was performed on the 7th day of treatment and showed improvement of the hemangioma in the vocal cord and nearby tissues (**Figure. 4**). The patient was discharged as no adverse

drug reactions were observed. The patient continued to be treated outpatient for 1 year and subsequent MRI confirmed that the lesion disappeared. Drug treatment was discontinued and the patient has remained asymptomatic and stable ever since (**Figure. 5**).

## 4. Discussion

Infantile hemangiomas are the most common benign tumors in children that are often undetected at birth and diagnosed between the first 4–6 weeks of life, with a maximum increase in size over the next several months [6]. Characteristically, the lesion proliferates until approximately 1 year of age, after which there is a period of no change in size, followed by a gradual shrinkage. Most hemangiomas are small, uncomplicated, and shrink spontaneously, and do not require treatment. However, in approximately 5%–10% of children, depending on the tumor's location, they can be associated with impairment of physical functioning and require treatment due to their rapid rate of proliferation, damage to surrounding tissues, and in rare cases, life-threatening conditions [7].

Before 2008, systemic or topical corticosteroids and interferon-α were used to treat infantile hemangiomas. However, systemic corticosteroids are associated with unwanted side effects like hyperglycemia, weight gain, behavioral abnormalities, adrenal and immunosuppression, hypertension, and growth failure, while irreversible neurotoxicity, particularly spastic bilateral paralysis, was reported with the use of interferon-α. Hence, usage of both drugs requires close observation and caution [8–13]. Since the report of successful treatment with propranolol in 2008, propranolol has become the first-line treatment of choice for infantile hemangiomas [5]. Propranolol is a nonselective beta-adrenergic receptor blocker that has been used for cardiovascular disease and anxiety disorders. The exact mechanism of action of propranolol in infantile hemangiomas is not yet well understood, but it is believed to cause vasoconstriction and cellular apoptosis, thus decreasing the expression of pro-angiogenic factors, and leading to improvement in clinical symptoms [14]. Propranolol was also known to provide a faster and better response with fewer side effects than systemic steroid administration [15,16]. Adverse effects of propranolol include bradycardia, decreased blood pressure, hypoglycemia, and exacerbation of lower respiratory tract infections, including bronchospasm, gastrointestinal events, and sleep disturbances. However, treatment with propranolol has rarely been discontinued despite these events [17].

The oral propranolol hydrochloride formulation currently used in the Republic of Korea has been available since June 2016 after approval by the Food and Drug Administration (FDA) in Europe, the United States, and the Republic of Korea. It is used as a treatment for infants in a syrup formulation that can be conveniently administered. In this case, the improvement in respiratory distress was thought to have been due to hemangioma shrinkage over time upon treatment. As infantile hemangiomas often resolve spontaneously, it is important to discuss the side effects and efficacy when choosing a treatment.

Imaging studies were performed to determine the cause of the recurrent respiratory distress, which revealed a small cutaneous hemangioma on the scalp that was deeply embedded in the subcutaneous tissue and extended from the head to the upper airway. Although rare, subglottic hemangiomas have been reported primarily in patients with cutaneous hemangiomas of the facial region [18]. In this case, the cutaneous hemangioma was found on the scalp in the cephalic region and appeared to be distant from the airway, but imaging studies confirmed that it was a subglottic hemangioma that extended from the subcutaneous tissue to the airway, thus causing dyspnea. This was a rare case of a cutaneous hemangioma found on the scalp that extends from the skull base to the subglottis. The patient developed dyspnea due to the proliferation of the hemangioma, which improved with oral propranolol treatment.

## 5. Conclusion

This case highlighted the need for imaging studies such as CT, ultrasound, and MRI to determine the extent of the hemangioma when cutaneous hemangiomas are observed in the head region and dyspnea symptoms occur.

## Disclosure statement

The authors declare no conflict of interest.

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Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

# Analysis of the Effect of Radiotherapy Skin Protective Agents on Skin Reactions in Patients with Nasopharyngeal Carcinoma Radiotherapy

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**Abstract:** *Objective:* To analyze the application effect of radiotherapy skin protective agents on skin reactions in patients with nasopharyngeal carcinoma radiotherapy. *Methods:* One hundred and twenty nasopharyngeal cancer patients admitted to the hospital from January 2017 to January 2023 were randomly divided into a control group and an observation group of 60 cases each. Both groups received radiotherapy. The control group received traditional intervention methods while the observation group received traditional intervention methods combined with radiation therapy and skin protective agent intervention. The skin reactions, pain, comfort, and quality of life were compared between the two groups. *Results:* Both groups of patients had skin reactions, but the severity of skin reactions in the observation group was lower than that in the control group ($P < 0.05$). On the last day of radiotherapy, the pain score of the observation group was lower than that of the control group, and the comfort score was higher than that of the control group ($P < 0.05$). The total quality of life scores of the patients in the observation group were higher than those in the control group ($P < 0.05$). *Conclusion:* In treating skin reactions in patients with nasopharyngeal carcinoma undergoing radiotherapy, the application of radiotherapy skin protective agents reduced skin damage and pain and increased their quality of life.

**Keywords:** Nasopharyngeal carcinoma; Radiotherapy; Skin reaction; Radiotherapy skin protective agent

**Online publication:** March 29, 2024

## 1. Introduction

Nasopharyngeal cancer refers to a malignant tumor that occurs in the nasopharyngeal mucosa, with squamous cell carcinoma being the most common. There are regional and gender differences between the incidence rates, whereby Southern regions have a higher incidence rate than Northern, with men at higher risk than women [1]. The early symptoms of nasopharyngeal cancer are relatively insidious. Hence, when most patients are diagnosed, their condition has already progressed to the mid-to-late stage. At this time, patients would need to receive radiotherapy. During radiotherapy, skin reactions may occur, which is a manifestation of treatment toxicity, with symptoms such as local pain and itching [2]. As symptoms worsen, adverse conditions such as blisters and ulcers can be observed, which reduces the comfort level and even affects the outcome of

radiotherapy. Clinical intervention is required to ensure that the radiotherapy plan is completed as scheduled. This article aims to analyze the prevention and treatment effects of radiotherapy skin protective agents on skin reactions during radiotherapy for patients with nasopharyngeal carcinoma.

## 2. Materials and methods

### 2.1. Information

One hundred and twenty patients with nasopharyngeal carcinoma were selected (admission time: January 2017 to January 2023) and randomly divided into a control group and an observation group, with 60 patients each. The control group consisted of 39 males and 21 females aged 29–70 years old, with an average age of 58.27 ± 8.16 years. For the TMN (tumor (T), presence of metastasis (M), extent of spread to lymph nodes (N)) stage, 3, 15, and 42 cases were in stages I, II, and III, respectively. The observation group consisted of 41 males and 19 females aged 31–69 years old, with an average age of 58.40 ± 8.03 years. For the TMN stage, 5, 12, and 43 cases were in stages I, II, and III, respectively. The two sets of data were comparable ($P > 0.05$).

### 2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Patients diagnosed with nasopharyngeal carcinoma and is an undifferentiated non-keratinized cancer; (2) Patients with clear indications and are willing to receive radiotherapy; (3) can communicate properly; (4) can cooperate to complete the scale; (5) patients with complete general information. Exclusion criteria: (1) Combined with other serious skin diseases; (2) serious infectious diseases; (3) mental illness or cognitive impairment; (4) those who quit halfway.

### 2.3. Methods

Both groups received a standardized radiotherapy regimen. Based on this, the control group received traditional intervention methods. When wet dermatitis was found in the radiation field, they were first cleaned with normal saline, followed by exposure therapy. According to the degree of skin damage and local infection, patients adhered to medical advice for drug treatment. Based on the control group, the observation group received a skin protective agent at the beginning of radiotherapy. Before using the drug, the skin in the radiation field was cleaned with normal saline. The drug was applied evenly and gently using a cotton swab. The drug was applied lightly to the skin once more than 2 hours before and after radiotherapy until the entire treatment was completed.

### 2.4. Observation indicators

The occurrence and degree of skin reactions between the two groups were compared based on the RTOG (Radiation Therapy Oncology Group) acute radiation injury grading standard [3]. Level 0 indicates no abnormal skin changes; Level I indicates the appearance of follicular dark erythema on the skin, local dry peeling, and reduced sweating; Level II indicates bright red erythema, or tenderness, wet peeling, and moderate edema; Level III indicates the appearance of fusion-like wet peeling and pitting edema outside the skin folds; Level IV indicates ulcers and oozing of blood, or necrosis.

The pain and comfort of the two groups on the first and last day of radiotherapy were compared. The VAS was used to evaluate the degree of pain, with scores ranging from 0–10, indicating no pain to worst pain [4]. Kolcaba's Comfort Status Scale was used to evaluate comfort, which included 28 items. Each item was scored from 1–4, with a total score of 28–112 points [5]. The higher the score, the higher the comfort level.

The quality of life of the two groups on the last day of radiotherapy was compared. The Cancer Treatment

Functional Evaluation Scale was used, which included four dimensions: physical, emotional, functional, and social/family status, corresponding to 7, 6, 7, and 7 items, respectively [6]. Each item ranged from 0–4 points, with a total score of 0–108 points. The higher the score, the better the quality of life.

### 2.5. Statistical methods

The data were analyzed using the SPSS 25.0 statistical software. The measurement data were expressed as mean ± standard deviation and compared using a *t*-test. Count data were expressed as % and analyzed using the chi-squared ($\chi^2$) test (the rank sum was used for the rank data test, Z). Results were considered statistically significant at $P < 0.05$.

## 3. Results

### 3.1. Occurrence of skin reactions

As shown in **Table 1**, both groups of patients had skin reactions, but the severity of skin reactions in the observation group was lower than that in the control group ($P < 0.05$).

**Table 1.** Occurrence of skin reactions between the two groups [*n* (%)]

| Group | Cases, *n* | Level 0 | Level I | Level II | Level III | Level IV | Total |
|---|---|---|---|---|---|---|---|
| Control group | 60 | 0 (0.00) | 30 (50.00) | 24 (40.00) | 6 (10.00) | 0 (0.00) | 60 (100.00) |
| Observation group | 60 | 0 (0.00) | 48 (80.00) | 12 (20.00) | 0 (0.00) | 0 (0.00) | 60 (100.00) |
| Statistics | - | | | Z = 3.036 | | | $\chi^2 = 0.000$ |
| *P* | - | | | 0.002 | | | 1.000 |

### 3.2. Pain and comfort score

As shown in **Table 2**, there was little difference in pain and comfort scores between the two groups of nasopharyngeal cancer patients on the first day of radiotherapy ($P > 0.05$). On the last day of radiotherapy, the observation group had lower pain scores and higher comfort scores than the control group ($P < 0.05$).

**Table 2.** Pain and comfort scores between the two groups (mean ± standard deviation, points)

| Group | Cases, *n* | Pain score | | Comfort rating | |
|---|---|---|---|---|---|
| | | First day of radiotherapy | Last day of radiotherapy | First day of radiotherapy | Last day of radiotherapy |
| Control group | 60 | 6.25 ± **1.18** | 3.32 ± **1.08** | 73.56 ± **5.15** | 80.27 ± **3.36** |
| Observation group | 60 | 6.19 ± **1.23** | 1.86 ± **0.41** | 73.40 ± **5.57** | 91.46 ± **4.10** |
| *t* | - | 0.273 | 9.790 | 0.163 | 16.351 |
| *P* | - | 0.786 | 0.000 | 0.871 | 0.000 |

### 3.3. Quality of life score

As shown in **Table 3**, the scores and total scores of each dimension of the patient's quality of life in the observation group were higher than those in the control group ($P < 0.05$).

**Table 3.** Quality of life scores between the two groups (mean ± standard deviation, points )

| Group | Cases, *n* | Physiological condition | Emotional state | Functional status | Social/family situation | Total score |
|---|---|---|---|---|---|---|
| Control group | 60 | 19.25 ± 2.05 | 15.31 ± 2.11 | 18.17 ± 2.14 | 19.35 ± 2.22 | 72.32 ± 4.19 |
| Observation group | 60 | 22.14 ± 2.16 | 17.27 ± 2.05 | 20.65 ± 2.01 | 22.65 ± 2.34 | 82.65 ± 3.37 |
| *t* | - | 7.517 | 5.161 | 6.543 | 7.925 | 14.881 |
| *P* | - | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

## 4. Discussion

The cause of nasopharyngeal cancer is currently unknown. It is mainly related to genetics, diet, environment, and other factors. For example, increased consumption of salty foods, such as salted fish and pickles, will increase the risk of nasopharyngeal cancer. Individuals who are exposed to an environment with high content of dust, formaldehyde, and other substances for a long time are also prone to nasopharyngeal cancer [7,8]. Studies have found that nasopharyngeal cancer is a relatively mild disease, with a close relation to Epstein-Barr virus infections [9]. The early symptoms of nasopharyngeal cancer are not obvious. As the disease progresses, symptoms such as headache, hearing loss, ear stuffiness, nasal congestion, and neck lumps can be observed. Currently, the most effective clinical treatment for nasopharyngeal cancer is radiotherapy, including chemotherapy, targeted therapy, immunotherapy, surgical treatment, and traditional Chinese medicine (TCM) treatment. Radiotherapy is the first choice for nasopharyngeal cancer as it can eradicate the tumor cells. However, during radiotherapy, skin and mucosal damage is likely to occur, causing great pain to the patient and affecting the treatment outcome.

Skin and mucosal damage caused by radiation is known as radiodermatitis. This happens when the skin exposed to the radiation field absorbs many high-energy physical radiations, directly damaging epidermal cells. However, when the radiation dose is between 20Gy and 40Gy, the basal layer stem cells will lose new ones. Cell regeneration ability is manifested as the continuous reduction of mature epithelial cells in the early stage, the expansion and tortuosity of capillaries, the occurrence of ischemic necrosis of small thrombus, and in the later stage, local epithelial shedding and ulcer formation [10]. If radiotherapy is performed under high temperatures, radiation dermatitis may appear within two hours. The intense pain will directly affect the patient's cooperation with treatment, thereby reducing the therapeutic effect of radiotherapy. Therefore, skin reactions need to be properly managed during radiotherapy. Traditionally, drugs that have a repair effect on epithelial tissue, such as recombinant human epidermal growth factor (rhEGF), are used to alleviate symptoms and reduce inflammation. However, this method is ineffective due to the complexity of the biochemical chain reaction of radiodermatitis.

The observation group was given radiotherapy skin protective agents based on the conventional intervention methods. The results showed that patients in the observation group had lesser skin reactions, lower pain scores on the last day of radiotherapy, higher comfort scores, and improved quality of life as compared to the control group ($P < 0.05$). Data show that using radiation therapy skin protective agents can reduce the degree of skin reactions of patients, actively relieve pain, and improve patients' comfort and quality of life during radiotherapy. Radiation therapy skin protective agents promote skin regeneration, balance skin moisture, prevent local cell damage, and facilitate epidermal cell repair. The main component of the skin protective agent is aloe gel. Aloe is a lily plant with detoxification and liver-drying functions. It is commonly refined into aloe vera gel, which is rich in a variety of natural moisturizing factors, such as complex polysaccharides and amino acids that can replenish lost water, facilitate the recovery of collagen function, and maintain the

skin in a smooth and tender state. In addition, the special substances in aloe gel will also inhibit the synthesis of melanocytes and are useful for whitening. Substances such as serine and glycine can resist radiation and promote skin metabolism. In addition, aloe vera contains high levels of human flavin glycosides, which can sterilize and inhibit bacteria, facilitate local metabolism, converge sores, prevent skin keratinization, and promote cell regeneration. Aloe vera gel can also enhance the ability of cells to resist oxidative damage. Hence, consistent use can delay skin aging. It is often used daily to treat allergies, acne, and other problems, due to its heat-clearing and detoxifying effects. Lanolin, another main ingredient in skin protectants, is obtained through processing and extraction from wool. It helps the skin become tender and smooth. Lanolin is contained in many skin care products, mainly in anti-wrinkle creams. Lanolin can replenish water, promote moist and smooth skin, and exhibit good anti-aging effects when the skin is relatively dry. Lanolin contains high vitamin E content, which can remove and resist harmful acid substances, promote skin elasticity, and delay aging [11]. The skin protectant was applied to the exposed skin on the first day of radiotherapy. It is simple to operate and can be easily cleaned. Furthermore, it can increase the skin's tolerance to radiation, reduce the degree of skin damage, relieve pain, and increase the patient's compliance with treatment.

## 5. Conclusion

The application of radiotherapy skin protective agents to patients undergoing radiotherapy for nasopharyngeal carcinoma reduced the degree of skin reactions, relieved pain, and improved their quality of life.

## Disclosure statement

The authors declare no conflict of interest.

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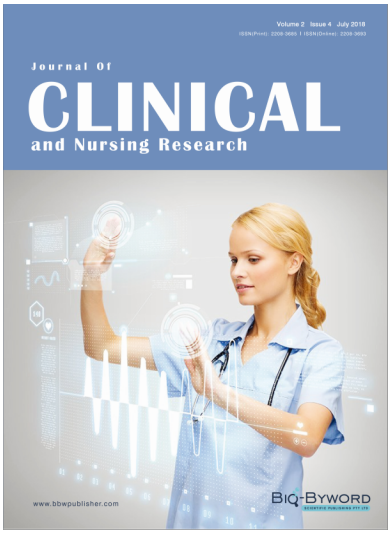


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