

Analysis of Treatment for Eye Cancer Based on Existing Materials

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Abstract. With the improvement of screening mechanisms for eye diseases and the popularization of cancer screening, more and more people discover that they have different types and degrees of eye cancers. These cancers can affect the skin of their eyes, may also make their vision decreased, and may even deprive their eyeballs. Besides, these diseases will affect patients' physical and mental health. Therefore patients want to find the most appropriate treatment to manage the disease. However, some treatments are may not so effective or suitable for each individual. Based on the existing literature, canonical analysis, clinical trial analysis and content integration were used to analyze the three effective and popular methods of treating ocular cancers. Studies have found that Surgical excisions, Chemotherapy, Immune Checkpoint Inhibitor therapy are effective in the treatment of eye cancers (squamous cell carcinoma of the eyelids, basal cell carcinoma of the eyelids, retinoblastoma, metastatic melanoma of eye and orbit), although some treatments do not have the most effective treatment for some cancers.

Keywords: Eye cancer, Surgical excisions, Chemotherapy, Immune Checkpoint Inhibitor Therapy.

1. Introduction

With the development of electronic equipment, such as television, mobile phones, DVDs, and so on, more and more symptoms and results of eye diseases are gradually revealed. Paul and his teammate's study showed that from 1991 to 1999, different eye diseases increased at least fivefold in the world, such as the percentage of glaucoma increased from 1.5% to 6.5% [1]. Due to the country's aging population, vision impairment (VI) and eye illnesses which are related to age are becoming much more common in mainland China. Because of this amazing rise of eye diseases, more and more attention has been paid to eye diseases. Families nowadays are paying more attention to their members' eye condition. The governments also publish various rules about eye diseases, to be more specific, the Chinese government and health policy makers suggested the establishment and development of management system of eye health in China to manage the durative of citizens' eye health and viability of treatment for different kinds of eye diseases with less expense of money in the conference of "Thirteenth Five-Year Plan for (2016–2020)" in which was talking about the national Eye Health [2]. To address the demands of the Chinese people's eye health, these systems are now developing a "Fourteenth Five-Year Project" which will benefit for national eye condition.

There are many eye cancers, such as squamous cell carcinoma of eyelids, basal cell carcinoma of the eyelids, retinoblastoma, metastatic melanoma of eye and orbit, and so on. As more and more people get checked for eye diseases, researchers have found that the prevalence of eye cancer is also increasing year by year, and eye cancer is the second most important factor affecting eye health and vision after myopia, which are becoming a common social concern among citizens. Until 2022, the incidence of eyelid tumors in the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight) shows that there were almost 82 136 patients with eyelid cancer. The incidence of cancer varied from 87.9 (basal cell carcinoma of the eyelids) to 25.6 (unspecified malignant neoplasm), 11.1 (squamous cell carcinoma of eyelids), 5.0 (sebaceous carcinoma), 4.1 (malignant melanoma), and 0.4 (melanoma in situ) per 100 000 population [3]. Some of them could oppress on the nerve which could block the line of sight, besides, some could increase high pressure in the eye which can result in vision loss and even blindness. Some kinds of eye cancers even metastasize

throughout the body, causing systemic cancer disease. These symptoms make people feel very alarmed and seriously affect people's physical and mental health, as a result, people want to find the appropriate treatment.

There are several treatments to deal with cancers, such as Chemotherapy, Surgical excisions, Immune Checkpoint Inhibitor Therapy, Photodynamic therapy, targeting single molecular abnormalities or cancer pathways and so on. However, to deal with these harmful factors, people want to find the most suitable and effective ways. The effects and limitations of different therapies in these cancers are not well understood. Therefore, this paper will study, integrate, and analyze some methods of treating eye cancer intensively, so that patients and even scientists can quickly find the best treatment for their patients. This study will first classify the three categories majorly which are the most effective treatments: Surgical excisions, Chemotherapy, Immune Checkpoint Inhibitor Therapy. Secondly, this paper will carefully analyze and explain the mechanism and principle of each treatment method, and make a specific analysis according to some diseases targeted by the treatment method. Based on personal opinion, this paper will make a vision for the future treatment of ocular cancer.

2. Surgical Excisions for Eye Cancers

Surgical excisions are the most basic and first choice of surgery for all tumors. The main method is to remove the affected area and the area that may metastasize, to obtain a result of avoiding tissue proliferation and deterioration.

2.1. Surgical excisions for basal cell carcinoma of the eyelids

Basal cell carcinoma (BCC) is the most common malignancy in human's especially white people. Basal cell carcinoma seldom metastasizes; therefore, death is low, but this cancerous condition has a high morbidity rate. In North America, its prevalence is increasing by up to 10% year, bringing the lifetime risk of basal cell carcinoma to 30%. Basal cell carcinoma incidence varies significantly by region. In south Wales, the predicted incidence of basal cell carcinoma which was standardized by age was 114.2 per 100 000 people in 1998. In Minnesota, USA, the total age and sex standardized yearly incidence was reported to be 146 per 100 000. At 726 per 100 000, the incidence is significantly greater in Australia. Due to the under-reporting of basal cell carcinoma to cancer registries, these numbers are probably an underestimate [4].

Additionally, the most common periocular cancer is basal cell carcinoma. Most typically, it happens between the sixth and seventh decade. A block or hyperplasia was the most frequent initial symptom, and symptoms related to the tumor lasted 20 months on average. The most frequent sites of involvement where the lateral can thus, medial can thus, upper lid, and lower lid, in that sequence, are most frequently seen [5]. Despite being a slow-growing tumor, orbital invasion can cause serious morbidity in the periocular area. Thus, basal cell carcinoma of the eyelids significantly burdens the world's healthcare systems. Additionally, individuals with this syndrome have a significant chance of acquiring additional basal cell carcinomas and other cancers. Biopsy is advised for all suspected lesions since clinical presentation might vary greatly. Individualized management is required, taking into consideration the patient's circumstances, the tumor's features, and the subtype of histology. There have been several suggested treatment options, however surgical excision with close attention to the excision margins has the best success rate.

Excision is controlled by systematically using frozen sections to remove serial layers of the afflicted organs and inspect microscopically the whole underside of every individual layers. Based on the cure rate for five consecutive years of 99% in 1,773 instances of the basal cell carcinoma and 98.1% in 213 cases of squamous cell carcinoma of the eyelids, Frederic et al. demonstrated the validity of surgical excisions [6]. In addition, of 273 cases of basal cell carcinoma affecting eyelids, 60% had the clinical diagnosis of John et al. confirmed. The clinical treatment in 80% of the cancers was excision simply. Eight patients required exenteration. For 209 patients, follow-up data was

gathered. 18% of patients reported complications, excluding recurrences. The risk of recurrence was 12%. Besides, one and a half of patients who required exenteration experienced a recurrence later on. A death rate of 2% about this kind of tumor was observed [7]. And some study shows that the patient will have a about 99% cure probability if basal cell carcinomas of the eyelid are completely removed as an initial surgery surgically [8].

The limited loss of healthy tissue that is possible thanks to the accurate identification and selective excision of the clinically surprising malignant outgrowths is also crucial. This preservation of healthy tissue enables several cutting-edge wound treatment methods. Therefore, the existing resection is not perfect and needs to be improved.

2.2. Surgical Excisions for Squamous Cell Carcinoma of Eyelids

Studies showed that in many parts of the world, cutaneous squamous cell carcinoma (SCC) is the most prevalent kind of skin cancer [9]. On the patients' bodies, any anatomical region can develop this malignancy. To be more specific, SCC would be located on the people's eyelids. Squamous cell carcinoma of the eyelids is an unusual but potentially lethal disease. About 9% of all patients' eyelids malignancies are squamous cell carcinomas, despite the fact that pathologists routinely overdiagnose them and confound them histologically with other benign entities. The elderly, fair-complexioned citizens with a history of prolonged sun exposure and skin damage are more likely to develop this lesion. Squamous cell carcinoma in the lids can present in a number of clinical ways, but it often begins as a painless, hyperkeratotic lesion that grows slowly and eventually ulcerates. Lower lid and lid margin involvement is more common. This potentially fatal tumor has the ability to metastasize to nearby lymph nodes or spread rapidly locally. The majority of studies believe that before invasive squamous cell carcinoma arises, intraepithelial squamous dysplasia and intraepidermal squamous cell carcinoma are the stages of squamous cell carcinoma that proceed [10].

Even though eyelid SCC can have a lot of negative effects on individuals, the prognosis is often quite good if it is caught early and treated well. It is advised to completely remove the tumor after receiving histology proof that it has been removed. A bad prognostic indicator that may call for postoperative radiation is perineural spread. Although it is an uncommon problem, orbital invasion can be efficiently treated with exenteration if detected early. Any suspicious cancer which grow on the eyelids should be removed or biopsy since presentation varies and a histological study is necessary for a precise diagnosis.

Surgical excisions for squamous cell carcinoma of eyelids are suitable for them to deal with this cancer. 51 instances were found in 50 individuals due to clinical investigation by Donaldson and his colleagues. There were 17 female patients and 33 male ones. The patient population's ages varied from 26 to 93, with a mean of 65. In 31 cases, the lower lid had the lesion, the upper lid five times, the lateral canthus six times, and the medial canthus nine times. Four individuals had perineural invasion, while three had orbital invasion, following the surgical excision procedure, which involved a thorough excision and histological confirmation of clean margins. Three patients required exenteration. No patients experienced distant or lymph node metastases. The tumor caused the death of one patient who refused treatment. 31.1 months on average were followed up [11].

Patients who have eyelid SCC but do not have a significant impact on them should be informed of the possibility of developing new or recurring tumors and urged to go to lifelong follow-up appointments. Prevention is still crucial for reducing the morbidity and mortality from these lesions [12].

3. Chmotherapy for Retinoblastoma

If patients do not receive better cancer treatment after the surgical excisions, most patients will be treated with chemotherapy next. There are three essential mechanisms of chemotherapy which include the principles of intermittent medication dose, the bactericidal action of medicines, and the prevention of the emergence of drug-resistant *Mycobacterium tuberculosis*. Since the introduction of

streptomycin in 1947, preventing the establishment of drug resistance has been the primary goal in the creation of medication regimens. Researchers have discovered that the therapy has a very high success rate in treating eye cancer [12].

Retinoblastoma (RB) is a severe form of juvenile and infant eye cancer. Furthermore, retinoblastoma was the first tumor to bring the genetic basis of cancer to light. The first described tumor-suppressor gene, RB1, which is where it starts, is mutated. The severity of the illness upon presentation determines the likelihood of survival and the ability to preserve eyesight. Even though the cause of retinoblastoma is well understood, the death rate is over 70% among the nations with low and medium incomes, where the most part of afflicted children reside. Progress is hampered by a lack of rigorous clinical trials to evaluate novel therapies, poor public and medical knowledge. The majority of the projected 9000 newly diagnosed patients each year will die, according to research conducted globally [11]. There are several treatments for Retinoblastoma including radiation, laser photocoagulation, cryotherapy, and chemotherapy. Research shows that chemotherapy is used as the first-line treatment for patients with this malignancy nowadays.

There are several ways to administer chemotherapy, including intravenous way, intra-arterial method, periocular way, and intravitreal treatment. The better choice of chemotherapy for delivery method relies on the lateralization and stage of the tumor. To be more precise, orbital RB, bilateral instances, and high-risk RB that require adjuvant preventative therapy are the situations when intravenous chemotherapy (IVC) is most frequently employed. To help preserve the globe and vision, it is used for chemo reduction in conjunction with focused treatment for intraocular RB. Prior to enucleation, IVC might manage orbital retinoblastoma in patients receiving therapy. Second, numerous studies have demonstrated the effectiveness of intra-arterial chemotherapy (IAC) as a main or secondary treatment for eyes with recurrent or residual. RB. Kaneko disclosed the selective intraocular injection of melphalan using a balloon catheter to block the internal carotid artery in the 1990s. Abramson et al. further improved this method by using supraselective IAC, which involves injecting melphalan into the proximal ophthalmic artery. Besides, IAC has a number of benefits, such as the ability to manage intraocular tumors, end RD, save the globe, and have few systemic adverse effects. Third, in cases when the vitreous seeds are chronic or recurring, periocular chemotherapy is employed as an additional treatment. By administering this chemotherapy, it is possible to reach the posterior portions of the eye with larger chemotherapy drug concentrations. Finally, eyes with chronic or recurrent vitreous seeds are the only ones who can get intravitreal chemotherapy.

Clinical trials demonstrate how highly successful these therapies are. First off, Narang et al. observed that 6 years after intravenous chemotherapy, 37% of eyes still had vision of 20/40 or better. This suggests that intravenous chemotherapy can effectively maintain visual acuity [10]. Second, in terms of intra-arterial treatment, Shields and coworkers respectively 67 individuals have reported a 72% globe conservation rate with first therapy in 70 eyes, and they reported that regression of the solid tumor was accomplished in 94% of eyes, and subretinal and vitreous regression seeds was accomplished in 95% and 87% [13]. Third, according to studies, 39% of eyeballs with cancer would be preserved if periocular chemotherapy was combined with other treatments [14]. Finally, between 1946 and 2013 Smith et al. reported just 1 incidence of extraocular tumor expansion in their extensive meta-analysis of problems associated to 1,304 injections in intravitreal parts administered in 315 eyes with RB. This suggests a 0.07% chance that the extraocular tumor may spread [15]. Due to the high percentages of ocular survival and disease-free survival, several researchers noted that intravitreal melphalan is a successful therapy for vitreous seeding in retinoblastoma.

4. Immune Checkpoint Inhibitor Therapy for Metastatic Melanoma

Melanoma is a disease that is becoming more and more prevalent around the world., with a research estimated that during the year of 2002 there were 53 600 new cases and even 7400 deaths from melanoma in the United States of America [16]. However, increasing identification of the early stage disease, which is often curable through surgery, and better public awareness have resulted in a

general stabilization of melanoma-related rates of death. The clinical history of melanoma is often decided by its spread and relies on the patient's gender in addition to the thickness, ulceration, localization, and histology of the initial tumor. Although, metastatic melanomas have the potential to spread to any portion of a patient's body. Rare cases of metastatic melanoma that has spread to the eye or orbit often affect individuals who are at the end of their illness and have a short prognosis. Although the eye and orbit positions of metastatic melanoma are rare, they may also have an impact on the patients' quality of everyday life.

If the patients with the disease of metastatic melanoma still do not respond well after surgical excisions and chemotherapy treatment, they will be treated with Immune Checkpoint Inhibitor Therapies (ICIs). By the pathways of disrupting co-inhibitory signaling, immune checkpoint inhibitor therapies reactivate anticancer immune responses and encourage the removal of tumor cells by the immune system. Immune suppression is linked to the development and spread of cancer. Through different kinds of methods, which including immunological checkpoint pathways activation, which inhibits anticancer immune responses, tumor cells avoid immunosurveillance and advance. Besides, an enormous and significant improvement in the treatment of cancer was made possible by monoclonal antibodies that target immunological checkpoints.

The patients' immune system perceives a risk mark and is triggered by inborn marks to fight against the threat throughout the initiation phase and activation phase of immune responses, whether they are meant to combat infections or malignancies. Although the reaction is essential for management of infections and cancer, it must be stopped after the threat has been eliminated since continued activation ultimately results in significant tissue damage. Thus, after every immune system activation, there is a phase known as the termination phase, in which endogenous immune suppressor molecules turn down the immune system to prevent any unfavorable consequences. To boost the appearance and effectiveness of cytotoxic T lymphocytes (CTL) against malignancies, therapeutic techniques in the case of cancer immune treatments traditionally promoted the start and activation of immune responses. Immunological checkpoint blockade, in contrast, concentrates on stopping immunological responses by impeding immune suppressor molecules. Thus, it stops immune responses from coming to an end or even awakens CTLs that are worn out during an immunological response [17]. Additionally, although some immune checkpoint inhibitors are still in clinical studies, others have already been authorized for use in certain cancer therapies. To be more specific, Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two inhibitory molecules that have received substantial interest since they are the early immune therapies that dramatically increase survival in patients with metastatic solid cancer. And patients with metastatic melanoma were the first to be examined for and given approval for CTLA-4 or PD-1 inhibition.

Despite the fact that individuals with widespread metastases and a very limited life expectancy typically develop metastatic melanoma to the eye and orbit during the latter stages of the disease, these cases do happen. The Immune Checkpoint Inhibitor therapy could still reduce the symptoms of this cancer and protect the patient's vision and even the function of eyes. Bennett and his teammates prove this hypotheses by their clinical research. They reported two individuals with conjunctival melanoma that has spread locally for whom the only option for final surgery was an orbital exenteration, which would result in a total loss of vision and significant facial deformity. As an alternative, immune checkpoint inhibitor treatment was used to treat both individuals. One patient had a conjunctival melanoma that nearly completely disappeared after receiving neoadjuvant pembrolizumab treatment for around 12 months. A full pathologic response and pigmented macrophages were seen in many surgical biopsies of very minor residual pigmentation. When ipilimumab and nivolumab were used in conjunction for 5 months to treat the second patient's locally progressed and metastatic conjunctival melanoma, considerable conjunctival mass shrinking was seen, allowing the eye and ocular function to be preserved [18].

5. Conclusion

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Although Surgical excisions, Chemotherapy, and Immune Checkpoint Inhibitor Therapy are effective solutions to therapy the cancers, these solutions should be chosen according to the specific analysis of specific patients. Some patients' diseases may not be suitable for the treatment of this three treatment method. Some may also need to choose a more appropriate treatment for personal reasons, such as economic, religious, and other reasons.

Some treatment methods have not become more effective or suitable for all patients. Besides, some treatments don't have more clinical trials to prove their effectiveness. As a result, scientists still need to conduct further analysis and research.

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