Targeted Intraoperative Radiotherapy (TARGIT-IORT) in Breast Cancer Surgery

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Abstract. According to the WHO, breast cancer (BC) has become the largest increase cancer in the world. The vast majority of cancers require radiotherapy and it is the mainstream treatment modality. Although there are numerous treatments, it still does not have a suitable one because of the side effects of radiotherapy. To reduce the harm to the body, people are attending to find a fewer side-effect one. Nowadays, the intraoperative radiation therapy（IORT）is starting to come into its own. TARGIT-IORT is a type of accelerated partial breast irradiation (APBI). The differences between TARGIT-IORT and traditional radiation are the localized radiating space and radiotherapy can be administered during surgery. Researchers have now found that it has a precise radiation range and can be performed simultaneously during surgery. Besides, it performs even better than traditional radiation therapy in various aspects. This is certainly a new trend in breast cancer treatment. TARGIT-IORT is expected to be the next trend in the treatment of BC.

Keywords: Breast cancer; TARGIT-IORT; targeted intraoperative radiotherapy.

1. Introduction

Breast cancer currently has the highest incidence rate in the world. So far, there have been many treatments for breast cancer, such as total mastectomy, breast-conserving therapy with external beam radiation therapy (EBRT) and so on. TARGIT-IORT is a relatively new form of treatment appeared these years. Under the same anesthetic, after the tumor is removed, using the spherical applicator employed for breast irradiation with low-energy photons (low keV X-rays) and high-energy electrons. The diameter can be varied from 1.5 to 5cm with an increase or decrease range of 0.5cm [1]. The radiation intensity can be changed by the size of the tumor. Due to its convenience and effectiveness of treatment, TARGIT-IORT has been used in many cases of breast cancer. More and more studies have been conducted to better understand the pros and cons of this procedure. This paper will analyze TARGIT-IORT in terms of strengths, limitations and future challenges.

2. Strengths

So far, TARGIT-IORT has a lot going for it. This method has its dominance and is not pale in comparison to traditional treatments in many aspects.

2.1. Protect the Nearby Tissues Compared with Postoperative Radiotherapy

As all know that radiotherapy can damage normal cells near the tumor because the radioactivity of rays. EBRT has its greatest drawback is that when getting EBRT may not avoid damaging other tissues. Especially accepting breast cancer may damage the lung or heart if the tumor is close to these organs. However, different from traditional methods of treatments like EBRT, which need patients to have postoperative radiotherapy for many times after surgery, IORT can protect the nearby tissues by using physical cover and its small-scale radiation probe. The accuracy of TARGIT-IORT also contributes to the protection in surgery. Because breast cancer is not sensitive to low dose radiotherapy, IORT can realize its strength by single high-dose radiotherapy. EBRT is not able to kill tumor cells that cannot be seen on imaging scans, but during the operation, doctors can use imager to determine the precise location of the tumor. By doing this, tumor cells missed by tumor clearance can be minimized using imager and TARGIT-IORT to ensure a complete sweeping of tumor cells. Also,

because of the probe have only several millimeters in width, so it can be used in small wounds and have a great range of application.

2.2. Having a Better Quality of Life

As treatment techniques become more sophisticated, the quality of survival after treatment has become one of the primary topics of concern. Analyzing the quality can be divided in 5 aspects to discuss: global health status, restrictions in daily activities, general pain, breast symptoms and arm symptoms. Constant pain after the treatment of breast cancer is still a notable issue, and it is also an important point to evaluate the quality of life for female who accepted breast cancer treatment [2,3]. According to research of Welzel, in the aspects of restrictions in daily activities, general pain, breast symptoms and arm symptoms, TARGIT-IORT shows the best performance compared with EBRT. In the latter three aspects, the mean number of TARGIT-IORT is lower than the EBRT about 10-20. Global health status does not have a statistical linkage with quality of life [4]. This conclusion means that under the same condition, choosing TARGIT-IORT may let the patients have a better quality of life and reduce the pain and other symptoms than EBRT, which can make the patients go back to work or family more quickly. It is a time-saving choice. And because choosing TARGIT-IORT can improve the quality of life, it can reduce the anxiety of patients to a certain extent.

2.3. Having no Tangible Difference in Regional Recurrence Risk

Regional recurrence is a dangerous for patients because the environment of the breast is not perfect for another surgery, so patients usually take endocrine therapy to avoid regional recurrence. A new type of treatment must pass the clinical trial of regional recurrence and make sure it has an equal or diminishing regional recurrence. Otherwise, it could not be used widely in clinical.

According to the University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, at 5-year follow-up, risk of local recurrence with TARGIT was similar to EBRT when all patients were analyzed. The risk of local recurrence of TARGIT was 1.1% compared with the risk of EBRT which is 0.9%. It is obvious that the result of 0.3% variance rate between the two treatments may not make sure TARGIT has a more dangerous circumstance under regional recurrence than EBRT.

In addition, the distant recurrence and other recurrence have not much difference. They are 0.7% and 0.5% relapse rate of TARIT more than the EBRT [5].

These data have convinced that there are minor distinctions between the two treatments. The therapeutic effect of TARGIT can be the same with traditional EBRT treatment under suitable conditions.

2.4. Excellent Performance in Survival Rate

According to the WHO, in the year of 2020, there are about 685000 people died from breast cancer. Finding a new method to increase the survival rate of breast cancer is undoubtedly one of the things to watch for at the moment. TARGIT-IORT can achieve this standard.

The survival rate without local recurrence in 5 years do not have a difference between TARGIT and ERBT even under different subtypes. The size or grade of tumor, the positive or negative of ER, PR, and Her-2 and the lymph node status do not have a significant statistical gap in Vaidya’s research [6]. Excluding other causes of death, avoid four local recurrences can prevent one breast cancer death [7]. This provides that the TARGIT has the same or even a better therapeutic effect and survival rate than ERBT.

2.5. Reducing Non-breast Cancer Mortality

To cure a breast cancer needs not only clear the tumor, but also prevent other complications arising from treatment. Undesired side effects may not be ignored in radiotherapy treatment especially other tissues effected by the irradiation. TARGIT-IORT has its advantages that can't be overlooked when

it comes to the side effects. TARGIT have a fewer 3 or 4 side effect than the EBRT. And also, it has a lower risk of cardiovascular death rate [5].

One of the most considerable advantages of TARGIT is that this treatment has a lower mortality of other causes. The deaths which were caused by the recurrence have no significant differences, but the mortality of other causes using TARGIT-IORT is smaller than EBRT. In the research, the total deaths from non-breast cancer using TARGIT-IORT is 45, but total deaths from non-breast cancer using EBRT is 74 [8]. Although the difference between the two data is not distant, it is only the date from 1851 people. If analyzing in the whole world using sufficiently large sample size, the conclusion would be more clearly.

According to the conclusion, TARGIT-IORT can be provided to those who have a family history of cancer to decrease the risk of suffering from other cancers arose by radiation. Also, it can be provided to the patients having heart disease or cardiovascular disease to avoid causing or aggravating the condition.

Patients who need to take X-ray examination frequently can also be considered in the range that is suitable for TARGIT-IORT because of its systemic or local side effects of X-ray.

2.6. Having a Superior Cosmetic

With the development of the society and the innovation of technology, more and more female who suffer from breast cancer request an aesthetic of shape and form of their breast during the surgery. There is evidence that using TARGIT can have a more superior cosmetic than using EBRT because the radiation-induced change in color and shape [9]. TARGIT-IORT has a smaller radiused area compared with other radiotherapy treatments. The rate that appears excellent or good standard (similarity to pre-treatment) of the aesthetic of breast in TARGIT treatment is more than twice as much in ERBT treatment [10]. No matter if the patients should have EBRT after the surgery or not, it is possible that the cosmetic of breast would be better than the patients who have the whole breast radiotherapy only. The minimally invasive incision and the hidden location chosen for the procedure adds even more to a woman's confidence. The integrity of the breast for female can affect not only their satisfaction of their sex life, but also their self-respect in the society.

2.7. Requiring no Additional Radiotherapy after TARGIT-IORT

The current mainstream treatment for breast cancer requires patients to undergo extracorporeal radiotherapy after surgery. This may waste a lot of time and money for the patients. It is also a waste of labor and a pollution of the environment because of the CO2 emissions from travelling from homes to the hospitals or treat centers. TARGIT-IORT can address the problem effectively due to its efficiency.

Research has found that 80% of the patients can avoid additional radiotherapy after TARGIT-IORT. This can give patients more facilities in both physical and finical areas. It can reduce personal cost including the travelling fares and follow-up treatment costs because most of the patients live far away from the treatment center[8]. Also, reduce the times for the patients to go to the hospital or center can also save human resources. Doctors do not need to give extra radiotherapy operation and clinical attention.

It is also time-saving due to the no additional treatment and intraoperative radiotherapy can reduce the time on travelling. In Coombs’s research, patients who have accepted TARGIT-IORT save an average of 11-11.2 hours over patients who have accepted EBRT. And can reduce the emission about 87 to 25kg on carbon dioxide. It is not only economy for patients, but also for the environment [11].

Besides, because TARGIT-IORT mostly doesn't require a follow-up visit to a hospital or center for radiotherapy, it can effectively avoid the contact of person-to-person. During the period of outbreaks of infectious diseases, for example the COVID-19, this method can efficiently reduce the rate of infection.

From a long-term perspective, TARGIT-IORT can be a way to conserve natural and medical resources.

As a conclusion, the advantages of TARGIT-IORT can be stated to the patient. Firstly, the therapeutic effect of TARGIT-IORT is the same as ERBT and even less toxicity. The tissues can be protected during the surgery. Using the TARGIT-IORT can reduce other complications without increasing mortality rates. Even more, it has an excellent cosmetic effect which would be better than traditional treatments. Also, saving time is an advantage that may not be ignored. If there are other risks that have been found during the course of the surgery, patients can also have postoperative radiotherapy after the surgery which means that the treatment program can be changed but not limited to only TARGIT-IORT to guarantee the therapeutic effect. Patients can decide according to these statements whether they can accept the relatively newer treatment.

TARGIT-IORT now also have a complete website which was established by the UK(www.targit.org.uk). Patients can get newly information of treatments and technology, find the nearest treatment center, and even calculate the travel-saving if choosing the TARGIT-IORT. This user-friendliness certainly adds a great deal of goodwill to patients choosing this treatment. Patients are able to get almost all information whatever they want to know before surgery.

Doctors can also give different treatment advice depending on patients' career and family disease history. The dominances of TARGIT-IORT can reduce the pressure of patients. Because of the good survival rates and solutions, patients can be relieved of their psychological burden to some extent. Less severe psychological stress has a favorable effect on the patient's prognosis.

3. Limitations

Despite its advantages, TARGIT-IORT have its inferiors. The main focus is on economic issues and recurrence rates for specific pathology types.

3.1. Relapse Rate of DCIS

Generally, the regional recurrence does not have a difference between EBRT and TARGIT-IORT, one subtype of breast cancer has a statistical discrepancy in relapse rate. The ratio of DCIS (ductal carcinoma in situ) to invasive recurrence was higher in the TARGIT-IORT arm (12:32) compared with the EBRT arm (1:19) [7]. Although the mortality rate does not have a statistically significant difference, but the recurrence showed a difference. If its recurrence as an aggressive cancer, the patient needs additional treatment such as radiotherapy or hormone therapy. Sometimes ever worse, so the patients need to get another surgery.

Although TARGIT-IORT and EBRT have a discrepancy of relapse rate in DCIS, overall survival was not affected in any way in TARGIT-IORT. As a result, when choosing the treatment solutions, doctors should take the typing of cancer into consideration. Optioning carefully when facing DCIS. More studies should be explored in this field.

3.2. Finical Problem

When a new technology wants to hit the market and become popular, the economy will always restrict some conditions.

From a general view, determination of target area location and dosage delivery relies heavily on the physician's experience. TARGIT-IORT was first used in the year of 1998. It means that this technology has only appeared for 25 years, and not all countries have this technology. Despite the fact that the progress of the surgery does not have a big distinct with traditional ones, training the doctors to be experienced may cost a lot of money and time, which means that it should be supported by not only hospitals but also the government.

Another cost is that the machine and technology is not easy to produce. The economic cost of this technology is too high and the clinical trial pass rate is too low, so many companies are reluctant to look into it. And this has led to the technology becoming more and more expensive. The price of the machine for example, the Photon Radiosurgery System (PRS) is not affordable for most treatment centers. Most areas do not have a condition to establish this treatment. There are only 250 centers of

35 countries that had taken part in the related researches of TARGIT-IORT, and most countries are from Australia, America and Oceania. Under the situation, the conclusions on the related fields do not cover all countries and areas. It has certain regional limitations. The data also reflects that not all countries can afford the coast of the technology. Most of them are developed and some developing countries.

Besides, operating theatre renovation should be done in parallel to avoid dangerous factors to doctors. The use of TARGIT-IORT means that the doctors would be exposed to the radiation. It is unsure whether the operators may accept more radiation or not. The health of the operators should also be taken into account.

In addition, the surgery of TARGIT-IORT would not be cheap because of the costly technology and consumables. Patients can choose the most suitable treatment program according to the state of an illness and economic condition.

4. Challenges

Till now, TARGIT-IORT is still unfamiliar in some fields. More aspects are waiting to be discovered and the healing effect in various scopes of application needs to be studied further.

4.1. Breast Density

The human breast consists of 4 main tissues: fibrous glandular tissue and adipose tissue. The images of these two tissues show up differently under radiography. On X-ray examination, fibrous glandular tissue appears to be dense, but adipose tissue is not. The ratio of the amount of dense tissue to the amount of non-dense tissue in the breast is often referred to as "breast density". Body Mass Index, short for BMI, is a commonly used and important measure of standard in the human body. It is popular not only among medical sector, but also familiar with the public. It is also simple to calculate, i.e., BMI = weight (kg) ÷ height^2 (m^2). If the value is less than 18.5 indicates underweight and a value greater than 28 indicates overweight. This calculation is somewhat reflective of the percentage of body fat in the total. Because the human breast is relatively simple in composition, to some extent the value of BMI reflects the percentage of fat in the human breast. Also, the value of BMI is an important principal for cancer. A higher BMI value is connected with untouchable tumors in clinical examination [12]. In TARGIT-IORT, breast tissue affects the RBE value of low-energy X-rays, so more interactive breast density measurements can also be used to adjust for variations in a patient's prescribed dose. It would be more convenient if the value of BMI can be a criteria for choosing whether to undergo TARGIT-IORT [13].

4.2. Triple Negative Breast Cancer

Triple negative breast cancer (TNBC) is a special type of breast cancer. It is often categorized separately as a study due to its clinically specific gene expression. TNBC occurs about 10% in breast cancer. This type of cancer cell surface was negative for estrogen receptor ER, progesterone receptor PR, and Her-2 gene amplification. Because TNBC lacks ER, PR and Her-2 expression, it may not benefit much from endocrine therapy. Because of the higher recurrence rate and poorer survival rate, TNBC becomes the poorest prognosis subtype. However, there is not much researches focus on TNBC using TARGIT-IORT. If TARGIT-IORT have a significant cure effect on TNBC, it would be a giant leap forward the treatment.

4.3. Racial Differences

Statistically speaking, in researches of traditional operation methods, it convinced that the therapeutic effect is associated with races using the meta-analysis. This may be related to genetic issues, but no one has analyzed the more in-depth reasons for this. It may also have to do with economic differences and differences in healthcare policies, which are not very easy to go and collect data on. And there is a great deal of bias. Besides, there is still not clear whether the TARGIT-IORT

has a same conclusion to racial differences or not because the research may not collect the surgery distances. If it does not have a statistical discrepancy on races, TARGIT-IORT may become the preferred method of treatment for minority breast cancer patients.

4.4. Gender Differences

Breast cancer occurs not only in female, but also in male. Breast cancer accounts for 1% of the incidence of cancer in men and 1% of the incidence of breast cancer among the world [14]. Most treatments of male breast cancer were learnt from women's breast cancer treatment. But it different in genes and hormone levels. Whether TARGIT-IORT for breast cancer of male is useful is not clear nowadays.

5. Conclusion

TARGIT-IORT is now being chosen by growing number of patients suffering from breast cancer. It has the advantages of good cosmetic performance, less non-breast mortality and time saving. TARGIT-IORT is no less prognostic and therapeutic than EBRT. Although it shows a positive effect in many aspects, economic problems still may not be ignored. The implementation of this treatment program requires policy and financial support from the government. This is a long and arduous project. If TARGIT-IORT can be published in every district of a country, it would be friendly to the patients as well as the environment. Actually, it would be a finical-saving and efficiency in a long term. Patients have their own decisions to select treatment, and what should doctors do is to give most suitable advice and guarantee the most basic safety of life.

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