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SKIN TOXICITY AFTER HYPOFRACTIONATED RADIOTHERAPY IN THE COMPLEX TREATMENT PROGRAM OF BREAST CANCER

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Abstract

Background: Radiation therapy is a necessary component of breast cancer complex treatment program, that reducing the frequency of relapses and increasing the life expectancy of patients. Daily fractions use of 2 Gy to a total focal dose of 50 Gy is the traditional standard scheme for radiotherapy treatment. However, like any other treatment method, radiation therapy provides a variety of adverse effects on normal tissues in the irradiated field. Acute radiation reactions of the skin are one of the most frequent side effects of this type of treatment. A practical solution to the problem is development of acceptable treatment regimens to achieve better local control with a minimal risk of toxic effects for normal tissues.

The aim of the present study is the incidence assessment of skin toxicity after a daily using of 2.7 Gy to a total dose of 43.2 Gy to the patient's breast

Methods: Study design is non-randomized clinical trial. From 2014 to 2017 years, 160 women with breast cancers, who were treated by the hypofractionated radiation therapy after surgical operations. The skin toxicity was examined at the end of the treatment, 3 and 6 months after treatment by the international scale for assessing criteria of acute radiation reactions developed by the American Radiation Therapy Oncology Group (RTOG, 1995). Mann-Whitney U test was used for comparing acute toxicity rate between patients treated with hypofractionation and traditional radiotherapy. A p value of <0.05 was taken as significant. The whole analysis was performed with SPSS ver.20 software.

Results: It was designated that skin of the patients is well tolerated for hypofractionated radiotherapy, due to lower fractional doses of radiation it gives good results: more than 80% of patients had no toxicities at all with the treated schedule. The rate of mild toxicity (> grade 2) was minimum in these patients ($p=0.023$).

Conclusions: The use of hypofractionated regime of radiation therapy does not increase normal tissues damage and frequency of acute radiation complications. However, some toxic events may take time to develop.

Key words: *radiation therapy, breast cancer, hypofractionation, skin toxicity.*

Резюме

ОЦЕНКА ТОКСИЧНЫХ ЭФФЕКТОВ КОЖИ ПРИ ГИПОФРАКЦИОНИРОВАННОЙ ЛУЧЕВОЙ ТЕРАПИИ В ПРОГРАММЕ КОМПЛЕКСНОГО ЛЕЧЕНИЯ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

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Актуальность: Лучевая терапия является обязательным компонентом комплексного лечения рака молочной железы, снижая частоту рецидивов и увеличивая продолжительность жизни пациентов. Традиционной стандартной схемой проведения лучевой терапии является подведение 2 Грей ежедневными фракциями до суммарной очаговой дозы 50 Гр. Но, как и другие методы лечения, лучевая терапия может давать разнообразные побочные эффекты, действуя на нормальные ткани в облучаемом поле. Острые лучевые реакции кожи являются одним из наиболее частых побочных эффектов подобного вида лечения. Для решения данной проблемы необходимо разработать приемлемые схемы лечения для достижения лучшего локального контроля с минимальным риском возникновения токсичных эффектов у нормальных тканей.

Целью настоящего исследования является оценка частоты острых лучевых реакций кожи с использованием ежедневного фракционирования 2,7 Гр до суммарной дозы 43,2 Гр на область молочной железы.

Методы: Дизайн исследования – нерандомизированное клиническое исследование. За период с 2014 по 2017 гг. нами были проанализированы результаты лечения 160 пациенток с раком молочной железы, получившие гипофракционированную лучевую терапию после хирургического лечения. Исследовался кожный покров на наличие токсичного эффекта в соответствии с международной шкалой оценки критериев острых лучевых повреждений, разработанных Американской онкологической группой по радиационной терапии RTOG (Radiation Therapy Oncology Group, 1995) в конце лечения, спустя 3, 6 месяцев после лечения. Для сравнения острой токсичности был использован U-критерий Манна-Уитни между группами, получавшими лечение по гипофракционированной и стандартной схеме. При значении p менее 0,05 разница считается статистически значимой. Весь анализ был проведен с помощью программного обеспечения SPSS ver.20.

Результаты: Гипофракционированная лучевая терапия, вследствие меньших фракционных доз облучения на кожные покровы, дает хорошие результаты; более чем у 80% пациентов не было зафиксировано лучевых реакций. Средняя токсичность (> 2-й степени) была минимальной у этих пациентов (p = 0,023).

Вывод: Несмотря на теоретические и исторические предпосылки, о применении различных режимов лучевой терапии, которые могут увеличить частоту острых лучевых осложнений, как правило, при нашем опыте гипофракционирования не были увеличены данные показатели. Однако для проявления некоторых токсических явлений могут понадобиться десятилетия.

Ключевые слова: *лучевая терапия, рак молочной железы, гипофракционирование, острая реакция.*

Түйіндеме

СҮТ БЕЗІНІҢ ҚАТЕРЛІ ІСІГІ БАР КЕШЕНДІ ЕМДЕУ БАҒДАРЛАМАСЫНДА ГИПОФРАКЦИЯЛАНҒАН СӘУЛЕЛІК ТЕРАПИЯ КЕЗІНДЕ ТЕРІ ЖАМЫЛҒЫСЫНЫҢ ТОКСИКАЛЫҚ ҚАСИЕТТЕРІН БАҒАЛАУ

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Өзектілік: Сәулелік терапия - бұл сүт безі қатерлі ісігін кешенді емдеудің міндетті компоненті, рецидивтердің жиілігін азайту және пациенттердің өмір сүру ұзақтығын арттыру. Сәулелік терапия үшін дәстүрлі стандартты схемасы - 2 Гр күнделікті фракцияларды жалпы 50 Гр-қа дейінгі дозаға дейін жеткізу. Бірақ емдеудің басқа әдістері сияқты сәулелі терапия сәулелендірілген өрістегі қалыпты тіндерге әсер ететін әртүрлі жанама әсерлерді тудыруы мүмкін. Терінің шұғыл радиациялық реакциялары - бұл емнің түрінің жиі жанама әсері. Бұл мәселені шешу үшін қалыпты ұлпаларда токсикалық әсер минималды тәуекелімен жақсы локальды бақылауға қол жеткізу үшін қолайлы емдеу режимдерін жасау керек.

Зерттеудің мақсаты - тәуліктік фракциясының 2,7 Гр-ден беру көмегімен 43,2 Гр-ға дейін кеуде аймағының жалпы дозасын қолдану арқылы терідегі шұғыл радиациялық реакциялардың жиілігін бағалау.

Әдістері: Зерттеудің дизайны - бұл кездейсоқ емес клиникалық зерттеу. 2014 жылдан 2017 жылға дейін. біз операциядан кейін гипофракцияланған сәулелі терапия алған сүт безі қатерлі ісігі бар 160 науқастарды емдеу нәтижелерін талдадық. Біз 3 және 6 айдан кейін емдеу соңында Американдық Обыр тобы радиациялық терапия RTOG (Radiation Therapy Oncology Group, 1995) әзірлеген халықаралық шкаласы бағалау критерийлері шұғыл радиациялық жарақат, сәйкес тері улы әсері болуын зерттеді. Уыттылығын салыстыру үшін гипофракцияланған және стандартты схема өңделген топтары арасындағы U-Манн-Уитни тест пайдаланылды. P мәні 0,05-ден кем болса, айырмашылық статистикалық маңызды болып саналады. Бүкіл талдау SPSS 20 бағдарламалық қамтамасыз етудің көмегімен жүзеге асырылды.

Нәтижелері: Теріге сәулелену аз фракциялық доза байланысты гипофракцияланған сәулелі терапия, жақсы нәтиже береді; науқастардың 80% - нан астамы радиациялық реакцияларға ие болмады. Орташа уыттылығы (> 2-ші дәрежелі) осы науқастарға (p = 0,023) ең аз болды.

Қорытынды: сәулелік терапия шұғыл радиациялық асқынулардың жиілігін арттыруға әкеледі, түрлі режимдерін пайдалану теориялық және тарихи фон қарамастан, әдетте, бұл сандар біздің тәжірибеде көп болған жоқ. Алайда кейбір құбылыстар ондаған жылдар бойы дамуы мүмкін.

Негізгі сөздер: *сәулелік ем, сүт безі обыры, гипофракциялandыру, жедел әсер.*

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Introduction

Breast cancer is the most commonly occurring cancer in women, comprising almost one third of all malignancies in females. It is second only to lung cancer as a cause of cancer mortality, and it is the leading cause of death for Kazakhstan women between the ages of 40 and 55 [15]. The global incidence is expected to reach 2 million per year to 2030, due to the increasing number of proportions from developing countries [12].

Breast cancer occupies a leading position among all malignant neoplasms at women in the Republic of Kazakhstan. Specific gravity of breast cancer of the first and second stages was 80.6%, the mortality rate was 7.8 cases per 100 thousand population in the structure of oncological morbidity in 2014 [4].

Oncological and cardiovascular diseases cause death in 71% of all disease cases in Europe and Asia according to the World Health Organization data. According to forecasts, mortality and morbidity from malignant neoplasms until 2020 around the world will increase by 2 times [8, 19].

Diagnosis of breast cancer in the late stages of the disease leads to high mortality among the female population. Most likely, this is due to a low level of awareness of the population about the screening programs, the lack of oncological alertness. But, also, it is not excluded that the increase in mortality from breast cancer depends on inadequate approaches to special treatment.

In recent years, approaches to the treatment of breast cancer are changing. This fact is associated with an increase in the number of detected diseases at early stage due to diagnosis of screening programs. Thus, breast conserving procedures are increasingly being used; taking into account the smaller volume of tumors, new data on the molecular genetic structure of cancers and their effect on chemotherapy and targeted therapy have been obtained.

Choice of rational and adequate treatment of breast cancer is very complex. This is due to variety of options of the clinical manifestation and the course of disease and, therefore, necessity at planning of the treatment to take into account a variety of factors, any of which can be decisive in the prognosis of the disease [16, 20]. The current and opportunities for the treatment of breast cancer is determined by the clinical, morphological and biological characteristics of the tumor: the content of steroid hormone receptors, the expression of HER2neu (a membrane protein from the epidermal growth factor receptor family), the degree of malignancy depending on the proliferative index, the presence of signs of vascular tumor invasion, and also the prevalence of the process (stage of the disease), the age of the patient [6, 9].

A distinctive feature of the modern approach to the treatment of patients with breast cancer at early stage is performance of organ-conserving surgery. At the same time radiation therapy (RT) of the breast is carry out traditionally for improvement of the radicalism of organ-conserving treatment and ensure of local control. RT is distributed at the area of regional metastasis.

There are evidences that 5-year frequency of recidivisms reduces from 28 to 7% after providing of radiation therapy at breast-conserving treatment of breast cancer [2, 13].

However, it is necessary to take into account role of RT use that can leads to the development of the number of serious complications [1, 5].

Modern questions about the use of RT in the treatment of breast cancer of stage I-II are still unresolved. Decision of this problem passes in two directions: the definition of the indications to use and improvement of methods of radiotherapy. It must reduce the number of complications and increase the effectiveness of the treatment.

As the analysis of the literature data showed, all along the development of RT are constantly changing options and methods of radiation exposure [17, 21]. The current standard is the exposure of the rest of the breast and, if indicated, regional zones in the total focal dose of 2 Gy, 5 times a week (up to 50 Gy to the whole breast) and 10-16 Gy - local irradiation of the bed of the resected tumor. However, the question of the postoperative increasing in focal dose to the tumor after the traditional 50 Gy remains controversial. Thus, the Lyon study showed no difference in recurrence rate in patients who received (4.5%) and did not receive (3.6%) local irradiation of the tumor bed [3].

Decreasing of duration of radiotherapy leads to reducing of time and cost of treatment [14]. The risk of complications is related to the volume and kind of normal tissues, which are in the radiation

field, and to the number of fractions and / or the quantity of single and cumulative doses of RT.

In the Canadian study and in the START study patients were randomized to two groups that received conventional daily radiotherapy for 5 weeks and hypofractionated radiation therapy (HFRT) for 3 weeks. In the Canadian study, which included more than 1,200 patients, some patients received 42.5 Gy in 3 weeks, the other part - 50 Gy in 5 weeks (without further action). The frequency of local recidivisms was 6.2% and 6.7% for 10 years of follow up, regardless of age, size of the primary lesion and the type of systemic therapy. The study START compared patients who received 50 Gy in 5 weeks and 40 Gy in 3 weeks. Recurrences of breast cancer in the groups was 3.4%, with an average follow-up of 6 years [11, 18]. Cosmetic results and indicators of radiation reactions were better in groups with HFRT. The data suggest that current techniques of RT may provide an alternative to traditional radiotherapy.

Thus, despite the widespread use of RT in the treatment of early breast cancer, it is necessary to choose an adequate HFRT mode after breast surgery for maintenance the advantages of this approach, without increasing the incidence of toxicity to normal tissues. In connection with the development of HF regimes than radiotherapy is very urgent [10].

Our study is expected to obtain results that characterize the economic acceptability and clinical safety of the method in the Republic of Kazakhstan.

First implementation of the economic evaluation of the impact of the different radiation treatment variants is planned that takes into account key factors in life expectancy and disease-free interval.

The aim of the present study is to compare skin toxicity after HFRT at patients with breast cancer after surgical treatment using a regimen of 2.7 Gy per fraction to a total dose of 43.2 Gy with those of a group of patients treated with traditional fractionation schedule.

Methods

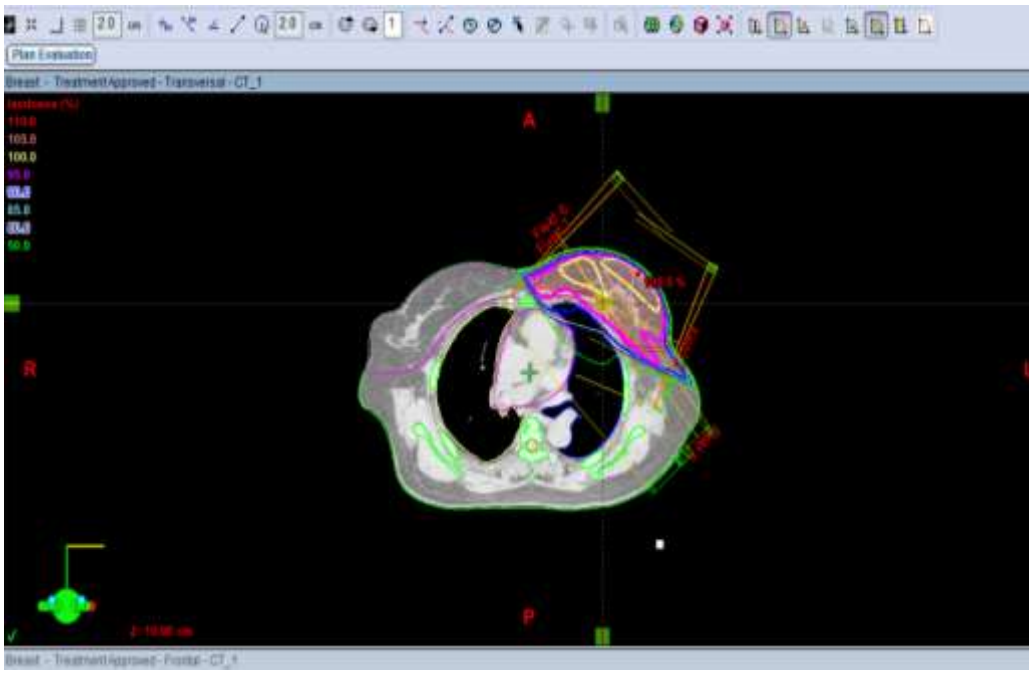
From January 2014 to July 2017, were examined 160 female patients who underwent surgical treatment for breast cancer in Regional Oncology center of Semey. Eligibility criteria include patients with histologically verified breast cancer undergone surgery, T ≤ 2 cm, with negative surgical margins. Patients received concurrent chemoradiotherapy, patients with cancer of other localization or with distant metastases, also with serious non-malignant disease (e.g. cardiovascular or pulmonary), severe mental or physical disorders were excluded from the study.

All patients signed written informed consent before start treatment following the rules of our university. There is a permission of Ethic Committee №5 from 12.03.2014.

All patients included in the study passed topometry preparation on the CT simulator GE OPTIMA ST580 (CT simulator is a computer X-ray tomography simulator for virtual modeling of the irradiation zone. It consists of a spiral computer tomography with a flat table deck, as well as a system of moving laser pointers). Three radiopaque points are applied to the patient's skin (at the center of the body, as well as at the intersection of laser beams on the lateral surfaces). The CT simulation is performed on a computer tomography with a step of 2.5-5 mm. The resulting images are transmitted to the Eclipse treatment planning workstation, where the radiologist is gradually delineating the critical organs (spinal cord, heart, and lungs, liver). The number of irradiation fields, the sizes and their mutual arrangement were selected individually for each patient, taking into account the anatomical structure. Radiation treatment performed by a distant method on gamma-therapeutic devices Terabalt (GK60T03, Czech Republic, 2008), Teragam (GIK-9-4, Czech Republic, 2006), and Truebeam linear accelerator (Varian medical systems, USA 2013).

All patients were planned for radiotherapy according anatomical points: the upper border is the level of the sternoclavicular junction; medial border is along the middle of the sternum; lower - 2 cm below submammary (transitional) folds; lateral – on 2 cm laterally to the palpable mammary gland tissue, usually along the mid-axillary line.

In addition, patients were also planned for RT to supraclavicular fossa when there was histopathological evidence of axillary node metastases. The treatment was planned with a goal of 100% volume of PTV to be covered by 95% isodose line as in Picture 1.



Picture 1. CT planning of RT of patient after breast-conserving surgery.

The skin toxicity was examined at the end of the treatment, 3 and 6 months after treatment by the international scale for assessing criteria of acute radiation reactions developed by the American Radiation Therapy Oncology Group (RTOG, 1995) [7]. Mann-Whitney U-test was used for comparing acute toxicity rate between patients treated with HFRT and traditional RT. A p value less than 0.05 were taken as significant. The whole analysis was performed with SPSS ver.20 software.

Results

Patients and disease characteristics are shown in Table 1. Median age was 56.5±10.9 (range 35.4-81.5). More often tumor histology type included invasive ductal (45.5%), the size of primary tumor is corresponded to T2, and stage was IIA 39.6% by TNM classification (65%). Also all patients were divided by type of surgical treatment, breast conserving surgery- 9.7%, mastectomy – 90.3%.

Table 1.

Patients and tumor characteristic, N (%).

Patients and tumor characteristics.		TRT	HFRT
Laterality	Left-sided	46 (57.4%)	42 (52.5%)
	Right-sided	35 (43.7%)	38 (47.5%)
Stage	I	5 (6.4%)	13 (16.3%)
	IIa	31 (39.6.%)	28 (35.0%)
	IIB	30 (37.7%)	26 (32.5%)
	IIIA	5 (4.7%)	4 (5.0%)
	IIIB	9 (11.6%)	9 (11.2%)
T size	T1	5 (6.3%)	11 (13.8%)
	T2	48 (60.0%)	52 (65.0%)
	T3	15 (18.8%)	10 (12.5%)
	T4	12 (14.9%)	7 (8.7%)

All patients were considered to have mild skin reaction with G1, moderate skin reaction for those with G2. The overall frequency of skin toxicity was reported in Table 2.

More than 80% of our patients had no toxicities at all with the treated schedule. The rate of mild toxicity (> grade 2) was low in these patients (p=0.23). None of our patients developed any symptomatic evidence of radiation pneumonitis at three months after completion of treatment. Then, the number of toxicity events is so low that no firm conclusion can be drawn from our data regarding the oncological safety of this procedure in patients.

Table 2.

Skin toxicity (RTOG scale) at 160 patients.

	Grade 0		Grade 1		Grade 2	
	HFRT	TRT	HFRT	TRT	HFRT	TRT
After RT	66(82.3%)	48(59.6%)	14(17%)	26(32.5%)	3(3.8%)	8(10.1%)
3 months	74 (93%)	67(83.2%)	7 (9%)	15(19.1%)	-	-
6 months	80 (100%)	80 (100%)	-	-	-	-

Discussion

Adjuvant HFRT for breast cancers has been practiced in the UK for a long time. The START Trials have proved the effectiveness of the same in their population [11]. Clinicians in Kazakhstan remain skeptical to adopt a hypofractionated schedule for their patient population; who they feel belong to a different race than our western counterparts. The mean age of presentation is also younger in this population and patients mostly present with advanced stage of disease. This study reports the preliminary results of 135 patients of breast cancer treated with the START Trial B hypofractionated schedule of 40 Gy in 15 fractions over 3 weeks for chest wall and breast conserved patients (which were followed by a boost) between May 2011 and July 2012. Of 135 patients, 45% patients had a breast conserving surgery whilst the rest had been treated with a mastectomy. Mean age of the population was 52 years (48 years in BCS patients and 56 years in mast patients) which is quite close to the mean age of the population of START Trial B of 57 years.

A detailed evaluation of the results indicates that not all tested hypofractionated regimens are equally suitable for clinical use. Although 39 Gy in 13 fractions was shown to be associated with less acute and late toxicity compared to conventionally fractionated RT, one has to keep in mind that a trend towards slightly increased ipsilateral breast cancer recurrences was observed in both trials (START Pilot and START A) testing this regimen [11]. Consequently, 39 Gy in 13 fractions should not be preferentially used. The same applies for the use of 42.9 Gy in 13 fractions, since this schedule resulted in significantly increased late toxicity. The remaining schedules, 40 Gy in 15 fractions, 42.5 Gy in 16 fractions, and 41.6 Gy in 13 fractions, are all suitable for routine clinical use.

The scope of this study is compromised by the small numbers of patients and short follow-up. However, dosimetry data suggest that accepted dose thresholds to the normal tissues, especially skin and subcutaneous tissues, can be achieved in most patients. Also, none of our patients developed any serious acute toxicity during treatment that required medical intervention or treatment interruption. In view of the obvious benefits of shorter time and costs and strong evidence of clinical equivalence to conventional fractionation, adjuvant HFRT should be strongly considered as an option for patients requiring postsurgical RT.

Conclusion

The results of our study suggest that patients with breast cancer can be safely treated with a shorter regimen of RT and our preliminary records appear to be in agreement with the literature data, showing that even for this type of low-risk cancer, quality of life can be improved and the use of resources of the RT center can be optimized. We also looked into the logistic benefits of a hypofractionated schedule. 9 fractions of RT saved per patient resulted in 540 fractions per year. This meant that additional patients could be treated leading to reduced waiting list.

In conclusion, moderately HFRT using schedules such as 43,2 Gy in 16 fractions administered within 3,5 weeks has been shown to be as efficient and safe as conventionally fractionated RT for most breast cancer patients who need adjuvant radiotherapy after breast-conserving surgery. In patients younger than 40 years, after neoadjuvant chemotherapy, and if regional lymph node RT is needed, cautious use is still recommended. In regard to breast cancer patients, concerns regarding late toxicity after hypofractionated therapy to the heart, lungs, axilla (lymphedema), and brachial plexus along with skin and breast cosmesis exist and limited published data in the postmastectomy setting are available.

The study is on-going to assess long term results

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