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Abstract

COMPARATIVE ESTIMATION OF MORBIDITY RATE AND DEGREE OF SKIN LESIONS DURING HYPOFRACTIONATED AND TRADITIONAL RADIOTHERAPY OF BREAST CANCER

Ainur S. Baissalbayeva, **http://orcid.org/0000-0002-7092-7448**

Tasbolat A. Adylkhanov, **http://orcid.org/0000-0002-9092-5060**

Yevgeniya O. Kossymbayeva, **http://orcid.org/0000-0003-2893-0384**

Olga B. Andreeva, **http://orcid.org/0000-0002-2802-9441**

Aizhan A. Abiltaeva, **http://orcid.org/0000-0002-0172-9202**

Semey State Medical University, Oncology and visual diagnostics department, Semey, Kazakhstan;

Background: Radiation therapy is a necessary step for the integrated treatment of breast cancer. The traditional scheme of treatment is the use of 2 Gray in 25 fractions to the total focal dose of 50 Gy. However, like any other treatment method, radiation therapy provides a variety of side effects on normal tissue in the irradiated field. To solve this problem it is necessary to develop suitable treatment regimens to achieve better local control with minimal risk on the normal tissues.

A variety of hypofractionated radiotherapy schedules has been proposed after surgery in the attempt to shorten the overall treatment time. The aim of the present study is to assess acute toxicity of using daily fractionation of 2.7 Gy to a total dose of 43.2 Gy to the whole breast in a monoinstitutional series.

Methods: Study design is non-randomised clinical trial. 132 Patients were evaluated for toxicity according to RTOG acute adverse effect criteria at the end of treatment and 3, 6 months after treatment. 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: Hypofractionation is very well tolerated; 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 results of our study, according to the large randomized trials, confirmed that hypofractionated is safe.

Key words: *radiation therapy, breast cancer, Hypofractionation, acute toxicity.*

Резюме

СРАВНИТЕЛЬНАЯ ОЦЕНКА ЧАСТОТЫ И СТЕПЕНЕЙ ПОРАЖЕНИЯ КОЖИ ПРИ ГИПОФРАКЦИОНИРОВАННОЙ И ТРАДИЦИОННОЙ ЛУЧЕВОЙ ТЕРАПИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ

Айнур С. Байсалбаева, **http://orcid.org/0000-0002-7092-7448**

Тасболат А. Адылханов, **http://orcid.org/0000-0002-9092-5060**

Евгения О. Косымбаева, **http://orcid.org/0000-0003-2893-0384**

Ольга Б. Андреева, **http://orcid.org/0000-0002-2802-9441**

Айжан А. Абильтаева, **http://orcid.org/0000-0002-0172-9202**

Государственный медицинский университет города Семей, Кафедра онкологии и визуальной диагностики, г. Семей, Республика Казахстан

Актуальность: Лучевая терапия является обязательным шагом для комплексного лечения рака молочной железы. Традиционной схемой лечения является применение 2 Грей за 25 фракций до суммарной очаговой дозы 50 Гр. Но как и любой другой метод лечения, лучевая терапия дает разнообразные побочные эффекты на нормальные ткани в облучаемом поле. Для решения этой проблемы необходимо разработать приемлемые схемы лечения для достижения лучшего локального контроля с минимальным риском для нормальных тканей.

Для сокращения времени лечения были предложены различные послеоперационные гипофракционированные режимы лучевой терапии.

Целью настоящего исследования является оценка острой токсичности с использованием ежедневного фракционирования 2,7 Гр до суммарной дозы 43,2 Гр на область молочной железы в моноинституциональном порядке.

Методы: Дизайн исследования – нерандомизированное клиническое исследование. 132 пациентов оценивали на токсичность в соответствии с RTOG критериями острых реакций в конце, 3, 6 месяцев после лечения. Для сравнения острой токсичности был использован U-критерий Манна-Уитни между группами, получавшими лечение по гипофракционированной и традиционной 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 очень хорошо переносится, 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 применениях различных режимов которые могут усугубить показатели ущерба нормальных тканей, частоты острых и поздних 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 БЕЗІ ОБЫРЫНЫҢ ГИПОФРАКЦИОНДЫ ЖӘНЕ ДӘСТҮРЛІ СӘУЛЕЛІ ТЕРАПИЯСЫНДА ТЕРІ ЗАҚЫМДАНУЫНЫҢ ЖИІЛІГІ МЕН ДӘРЕЖЕСІН САЛЫСТЫРМАЛЫ БАҒАЛАУ

Айнур С. Байсалбаева, **http://orcid.org/0000-0002-7092-7448**

Тасболат А. Адылханов, **http://orcid.org/0000-0002-9092-5060**

Евгения О. Косымбаева, **http://orcid.org/0000-0003-2893-0384**

Ольга Б. Андреева, **http://orcid.org/0000-0002-2802-9441**

Айжан А. Абильтаева, **http://orcid.org/0000-0002-0172-9202**

Семей қаласының Мемлекеттік медицина университеті, Онкология және визуальді диагностика кафедрасы, Семей қ., Қазақстан Республикасы

Өзектілік: Сүт безі обырының сәулелік терапия емдеу кешенді үшін қажетті қадам болып табылады. Емдеу дәстүрлі схемасы 50 Гр жалпы ошақты дозада 25 фракциялар 2 Грей пайдалану болып табылады. Алайда, кез келген басқа да емдеу сияқты, сәулелік терапия сәулеленген алаңындағы қалыпты тіндерге жанама түрде әсер етеді. Бұл мәселені шешу үшін қалыпты тіндерінің тәуекелі аз жақсы жергілікті бақылау үшін қолайлы емдеу схемасын әзірлеу қажет.

Уақытты үнемдеу үшін сәулелі терапияның әртүрлі операциядан кейінгі гипофракционды тәртіп қолданылды. Қазіргі кездегі зерттеудің мақсаты күнеклікті фракционды 2,7 Гр-ден суммарлы доза 43,2 Гр дейін моноинституциональді жағдайда сүт безі аймағына әсер етіп жедел улануды бағалау.

Әдістер: 132 науқасты RTOG критериясы бойынша емнен 3,6 айдан кейін уланудың жедел реакциялары бағаланды. Жедел улануды салыстыру үшін гипофракционды және дәстүрлі сызбамен ем алып жатқан топтарды U-критерий Манна-Уитни арқылы салыстырды. Статистикалық мәнде маңызды айырма құн p 0,05-тен кем болған жағдайда. Барлық анализдер SPSS ver.20 ақпараттық жабдықтардың көмегімен өткізілген.

Нәтижесі: 80% науқастарда сәулелі реакциялар тіркелмеген, себебі науқастар гипофракционированды сәулелі терапияны жақсы қабылдады. Орташа улану (> 2-дәрежелі) бұл науқастарда аз кездесті (p = 0,023).

Қорытынды: Біздің бұл тәжірибемізде теориялық және тарихи алғышарттарға қарамастан пайдалануға алынған әртүрлі режимдердегі қалыпты тіндерге жіті және кейінгі асқынулар кездеспеді, гипофракционды деректер көрсеткіштері ұлғайтылмады. Алайда соңғы онжылда бұл уланудың көріністері қажеттілікке жарар.

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

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Introduction

Breast cancer is of great importance throughout Asia including Central Asia, the incidence rate for example being recently found to be increasing in Kazakhstan [3,4]. Reported risk factors in the country include unfavorable living conditions, chronic stress, unilateral breastfeeding, breastfeeding less than 3 months and over 2 years, abortions, and hereditary predisposition [1, 2]. In addition, a direct strong correlation between the degree of contamination with high pollution emissions in the atmosphere from stationary sources and the incidence of breast cancer has been described [2].

Complex treatment of breast cancer contains surgery, radiation therapy and chemotherapy. The efficacy and safety of each step in treatment is the mandatory for success and it is characterized by lowering of recurrence rate and side effects. Surgery is directed to taking off the tumor, radiotherapy helps to inactivate micro metastases in tissues and lumena of lymph and blood vessels.

Radiotherapy (RT) as a part of breast-conserving therapy or after mastectomy has been proven to reduce the risk of local-regional recidive and to improve long-term breast cancerspecific and overall survival. As has been the common practice in the United States and Continental Europe, the majority of studies that demonstrated these benefits utilized daily radiation doses ranging from 1.8–2 Gray (Gy) [17]. Two more recent randomized trials from Denmark and British Colombia showed an improvement in overall survival with the addition of postmastectomy radiotherapy to tamoxifen in post-menopausal women and to chemotherapy in pre-menopausal women [2, 4, 5, 12, 14]. The same positive effect on overall survival was also documented in two metaanalyses including trials with more modern radiotherapy technique [9, 27].

Two key factors in these attempts have been: (1) advances in radiobiology allowing for a more precise estimation of equivalent dosing; and (2) advances in the delivery of RT that have resulted in substantially improved dose homogeneity in the target volume[9]. There has been an increasing recent interest in using hypofractionated breast RT because of its potential advantages. Patients' quality of life is often negatively impacted while they are receiving adjuvant RT [8] and a reduced number of treatments is more convenient, easier to tolerate, [24] and may reduce patients' feelings of anxiety and depression [8]. An hypofractionated course of therapy may also facilitate treatment in patients who live in remote areas, have significant difficulties with transportation, or are opposed to a longer treatment course for other reasons [10]. These considerations are particularly important in the elderly who comprise a significant percentage of diagnosed patients [1, 6, 11, 13, 16, 24]. Also, of note, is the significant potential cost savings that could be obtained by using hypofractionated treatment. Because of these benefits, many radiation facilities serving geographically dispersed populations in places such as Canada, Northern England and Scotland have used hypofractionated approaches [19]. The biological impact of hypofractionated treatment has been investigated in normal and tumor cell lines including breast cancer, and has been the subject of active clinical investigation in a variety of disease sites [3, 15, 20, 22, 23, 25, 28]. The differences in sensitivity to changes in radiation fractionation between normal and tumor cells can be explained by a linear-quadratic model, where an α/β parameter is inversely related to fractionation sensitivity and discriminates between "acute responding" normal tissue, such as skin and intestinal epithelium and "late responding" tissue, such as the spinal cord and kidney[15]. Late responding tissue accounts for long term radiation toxicity and is relatively more sensitive to increases in fraction size. Although most tumors are thought to be relatively insensitive to fraction size, with a/b ratios of 8 or more, in vitro and clinical data suggests that breast cancer may be more skin to certain acutely responding normal tissues, with an a/b ratio of approximately 4 to 5 [21]. These data have allowed for calculations of hypofractionated schemes (Figure 1) that are theoretically biologically equivalent to conventional fractionation in terms of expected tumor control, and the likelihood of late toxicity [26]. These 4 randomized controlled trials tested different schedules of hypofractionated RT against conventionally fractionated RT (50 Gy in 25 fractions in 3–5 weeks) [5, 8, 12, 22].

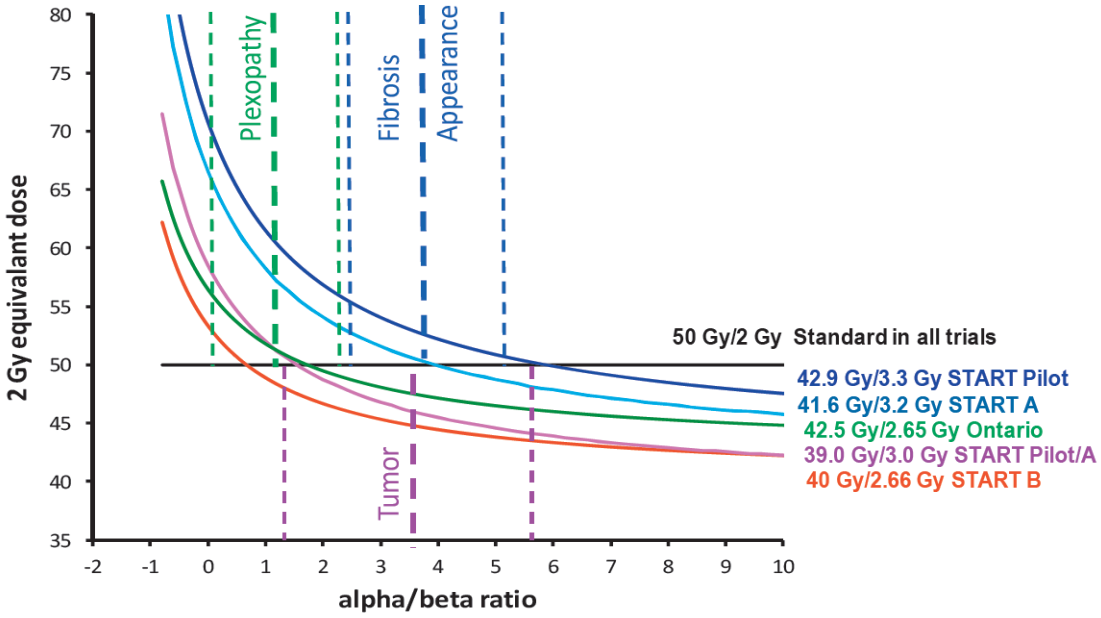


Figure 1 - Prediction of effects on tumor and normal tissues expressed as 2 Gy equivalent doses according to the linear quadratic model not considering repopulation. Conventional fractionation using 2 Gy per fraction (straight green line) compared to the hypofractionated RT schedules used in the different randomized trials (curved lines).

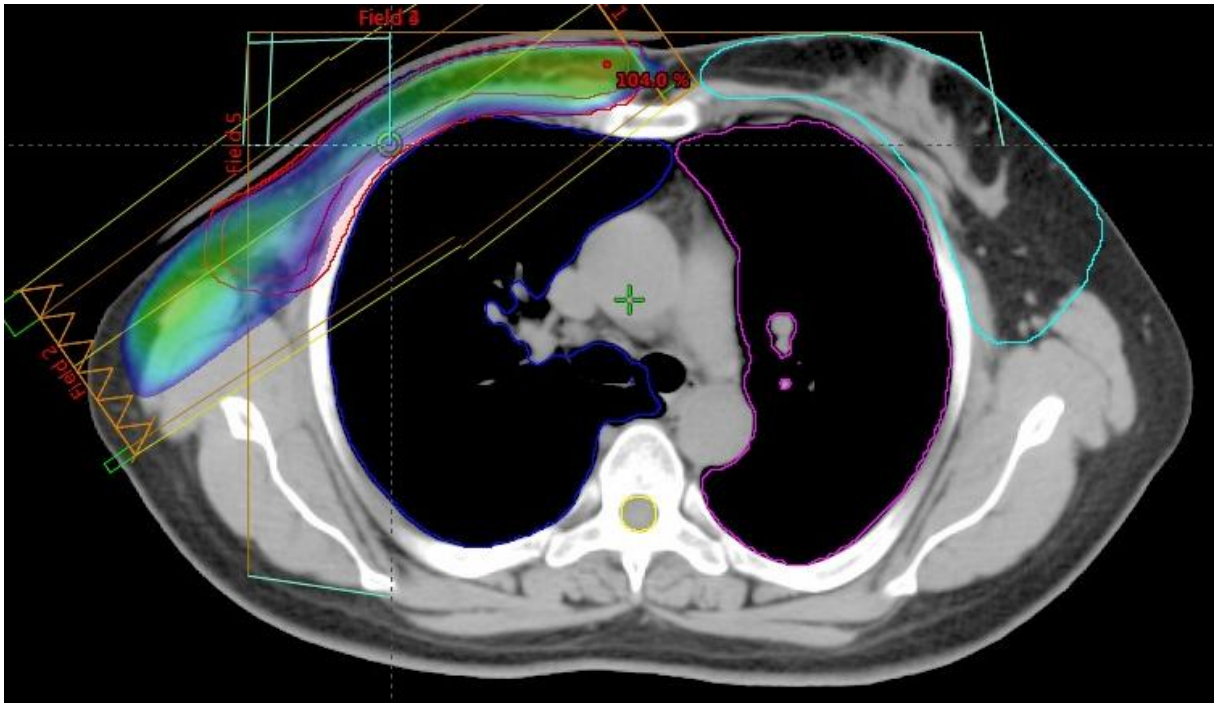
The aim of the present study carried out in a monoinstitutional clinical setting is to access acute toxicity of hypofractionated RT after surgical treatment using a regimen of 2.7 Gy per fraction to a total dose of 43.2 Gy with those of a group of patients treated with traditional fractionation schedule.

Methods. The design of study is non-randomized clinical trial. An analysis on the primary end point of the acute toxicity data was performed.

From January 2014 to May 2016, 132 female patients who underwent curative surgery for breast cancer. Eligibility criteria were: patients with breast cancer undergone surgery, T ≤ 2 cm, negative surgical margins. Patients with history of contralateral breast cancer, multifocal disease, serious non-malignant disease (e.g. cardiovascular or pulmonary), severe mental or physical disorders were excluded from the study.

Written informed consent was obtained from patients before start treatment following the rules of our university. Permittance of Ethic Committee №5 from 12/03/2014. All patients were planned for adjuvant HFRT to the chest wall.

In addition, patients were also planned for RT to supraclavicular fossa when there was histopathological evidence of axillary node metastases, and in scenario where neoadjuvant chemotherapy was administered prior to definitive surgery. All patients were immobilized while 'free breathing' using a thermoplastic mould in supine position with both arms extended above their head, abducted and externally rotated. Patients with inadequate lymph node dissection (less than 10 nodes examined pathologically) were also considered for RT to the supraclavicular fossa. Scar sites were marked using lead markers. Patients underwent CT simulation in the same position without IV contrast. The photon energy used was 6 MV. Beam arrangement included medial and lateral opposed tangential fields to irradiate the chest wall, with or without the use of a single anterior field (with a gantry tilt of 5-10 degrees to avoid the spinal cord and oesophagus) for the supraclavicular region using mono isocentric technique. 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 mastectomy.

Patients were evaluated for toxicity according to RTOG/EORTC acute adverse effect criteria at the end of treatment and 3, 6 months after treatment [7]. Mann-Whitney U-test was used for comparing acute toxicity rate between patients treated with hypofractionation and traditional RT. A p value less than 0.05 was taken as significant. The whole analysis was performed with SPSS ver.20 software.

Results.

Patients and disease characteristics are shown in Table 2. Median age was 56.5±10.9 (range 35.6-81.2). Most represented histology included invasive ductal (45.5%), the size of primary tumor

is corresponded to T2, and stage was IIA 37.9% by TNM classification (64.4%). Also all patients were divided by type of surgical treatment, breast conserving surgery- 9.7%, mastectomy – 90.3%.

Table 2.

Patient and tumor characteristic, N (%).

Patient and tumor characteristics		TRT	HFRT
Laterality	Left-sided	33 (45.8%)	27 (45.0%)
	Right-sided	39 (54.2%)	33 (55.0%)
Histology	Ductal carcinoma	35 (48.6%)	25 (41.7%)
	Lobular carcinoma	18 (25.0)	22 (36.7%)
	Mucinous carcinoma	4 (5.6%)	4 (6.7%)
	Medullar carcinoma	6 (8.3%)	2 (3.3%)
	Papillar carcinoma	4 (8.3%)	2 (3.3%)
	Others	5 (7%)	5 (8.3%)
Stage	I	4 (5.6%)	11 (18.3%)
	IIa	30 (41.7%)	20 (33.3%)
	IIB	25 (34.7%)	20 (33.3%)
	IIIA	4 (5.6%)	4 (6.7%)
	IIIB	9 (12.5%)	5 (8.3%)
T size	T1	4 (5.6%)	6 (10%)
	T2	43 (59.7%)	42 (70.0%)
	T3	11 (15.3%)	4 (6.7%)
	T4	14 (19/4%)	8 (13.3%)

For simplicity, patients were considered to have mild skin reaction for those with G1, moderate skin reaction for those with G2. The overall frequency of acute toxicity was reported in Table 3.

Table 3.

Acute skin toxicity (EORTC/RTOG scale) in 132 patients.

	Grade 0		Grade 1		Grade 2	
	HFRT	TRT	HFRT	TRT	HFRT	TRT
After RT	51 (81.7%)	43 (59.8%)	9 (15%)	22 (30.5%)	2 (3.3%)	7 (9.7%)
3 months	56 (93%)	59 (81.9%)	4 (7%)	13 (18.1)	-	-
6 months	60 (100%)	72 (100%)	-	-	-	-

Hypofractionation is very well tolerated; more than 80% of 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.

Discussion

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 [9]. 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; however, the most favorable observations were reported for the START B regimen [5].

The scope of this study is compromised by the small numbers of patients and short follow-up. However, dosimetric 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, according to the large randomized trials, confirmed that HFRT is safe. 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 hypofractionated RT 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.

Early oncological outcomes are encouraging as well. Long term data needs to be reported.

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Disclosure Statement

The authors have no conflict of interest to declare.

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Контактная информация:

Байсалбаева Айнур Сакеновна – PhD докторант по специальности «Медицина» Государственного медицинского университета города Семей.

Почтовый адрес: Республика Казахстан, 071400, г.Семей, ул. Абая 103.

E-mail: ainoor_baiss@mail.ru

Телефон: +77051253090