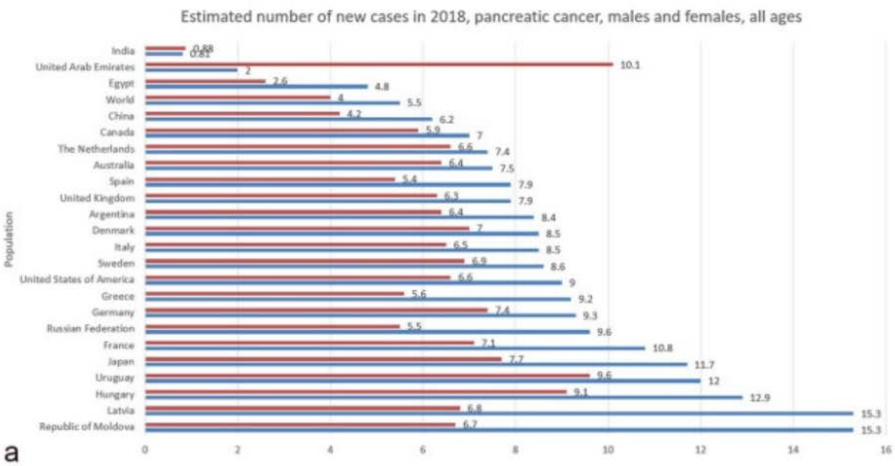
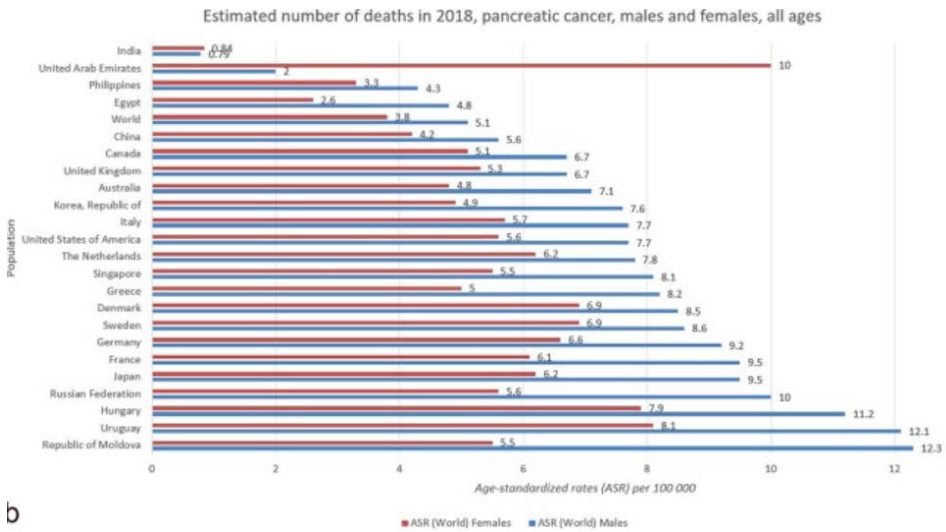
Предварительные результаты оценки эффективности и токсичности монохимиотерапии гемцитабином в комбинации с HIFU-терапией у ослабленных пациентов и пациентов старшей возрастной группы с нерезектабельным раком поджелудочной железы

МНИОИ им. А.П. Герцена - филиал ФГБУ
«НМИЦ радиологии» Минздрава России

ЗАБОЛЕВАЕМОСТЬ И СМЕРТНОСТЬ ОТ РАКА ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

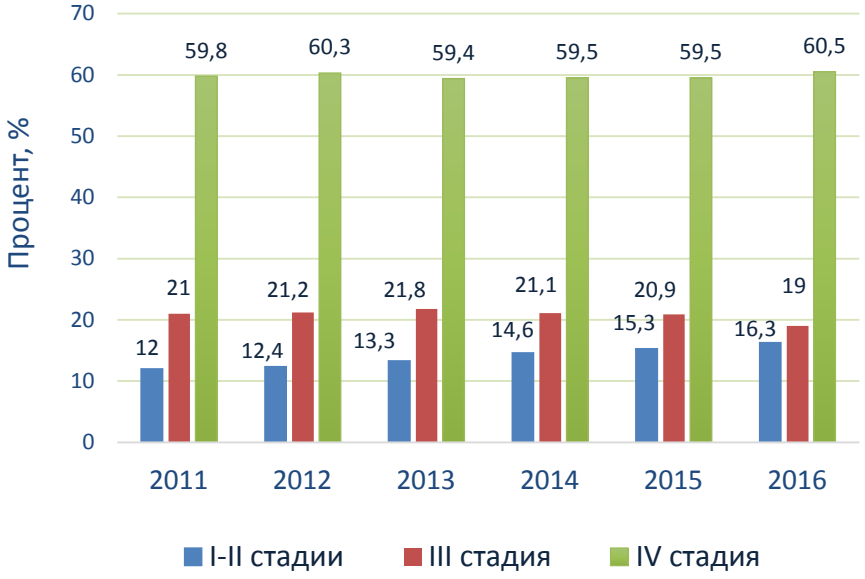




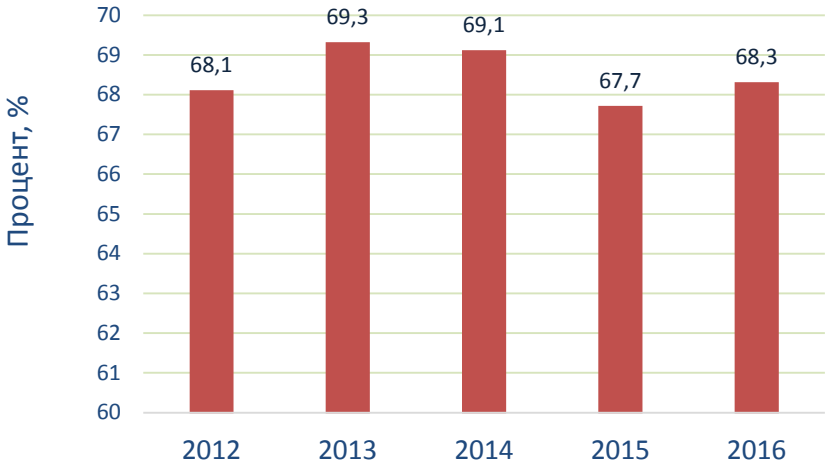
В 2018 году диагностировано 458,918 новых случаев рака поджелудочной железы - **2,5%** от всех ЗНО
Смертность от рака поджелудочной железы 432,242 смерти – **4,5%** от всех ЗНО в 2018 году, **7** место в мире
Таким образом рак поджелудочной железы по-прежнему является одним из ЗНО с самой высокой летальностью – общая 5-летняя выживаемость составляет около **6%** (2-9%).

Рак поджелудочной железы. Распределение по стадиям и летальность 2011-2016 гг

Распределение по стадиям пациентов с впервые в жизни установленным диагнозом ЗН поджелудочной железы в России в 2011-2016 гг., %



Летальность пациентов в течение года с момента установления диагноза «рак поджелудочной железы» в России в 2012-2016 гг., %



Особенности РПЖ: бессимптомное течение приводит к позднему обращению и диагностике заболевания на поздних стадиях

Злокачественные новообразования в России в 2016 году, под редакцией А.Д. Каприна, В.В. Старинского, Г.В. Петровой, , М.: ФГБУ МНИОИ им. П.А.Герцена Минздрава России. 2018

ВЫЖИВАЕМОСТЬ

ЗНО с крайне неблагоприятным прогнозом – соотношение смертность/заболеваемость 94%

Observed Survival For Pancreas

Cases Diagnosed in 1998 - 2002 Data from 1386 Programs [National]

Stage of Disease	ENTER	0.0 yr	1.0 yr	2.0 yr	3.0 yr	4.0 yr	5.0 yr
Stage 0	296	100.0	76.3	66.7	63.2	59.9	55.9
Stage I	4969	100.0	48.2	30.2	22.8	19.4	17.6
Stage II	5783	100.0	39.8	19.4	12.8	9.6	8.1
Stage III	7989	100.0	49.5	23.7	14.4	10.6	8.5
Stage IV	38085	100.0	16.0	5.1	2.8	2.0	1.6

2010 National Cancer Data Base/Commission on Cancer

SEER Relative Survival Rates by Stage at Diagnosis For Pancreas Cancer, All Races, All Ages, Both Sexes SEER 9 Registries for 1988-2003

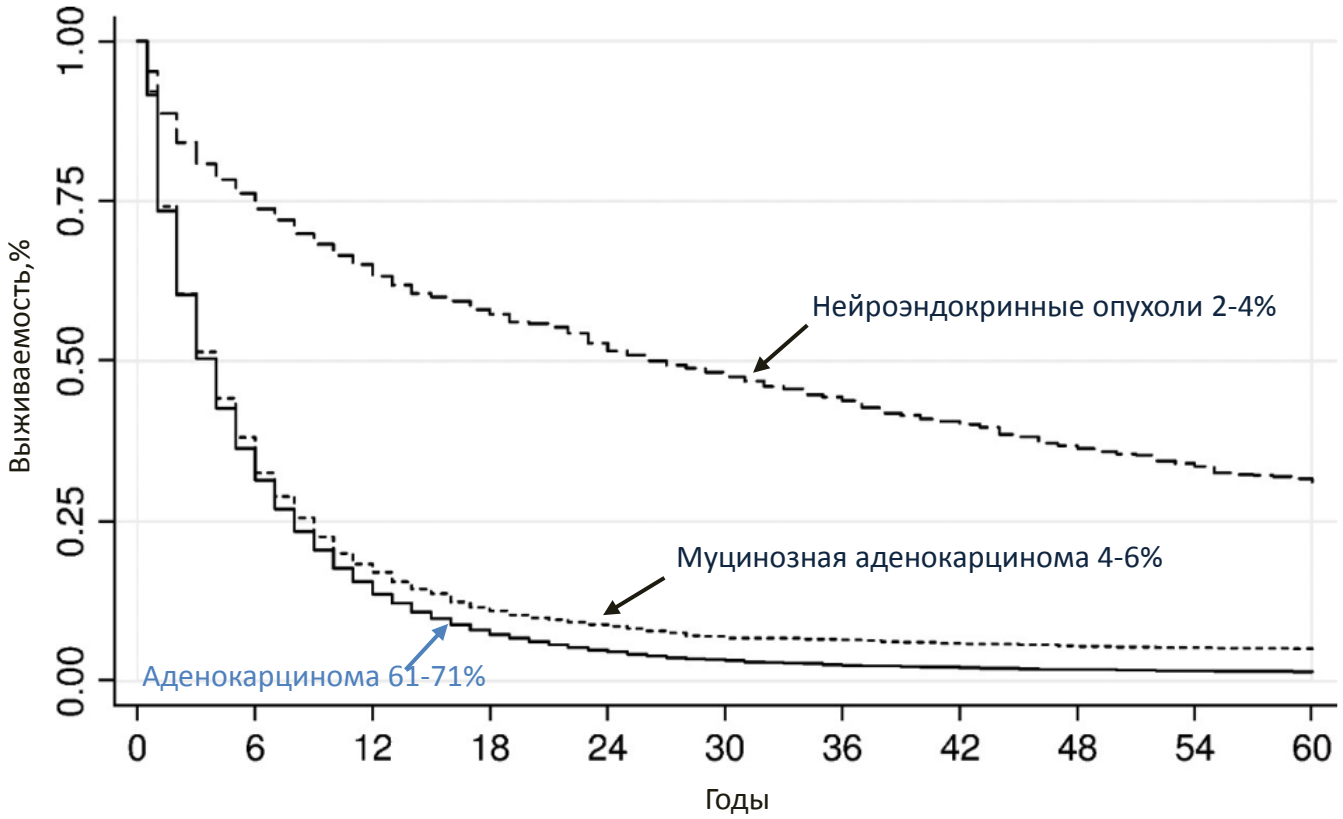
	Localized	Regional	Distant	Unstaged
Time zero	100.0%	100.0%	100.0%	100.0%
1-year	40.5%	38.0%	10.5%	20.8%
2-year	24.5%	16.7%	4.1%	9.3%
3-year	19.5%	10.5%	2.6%	6.2%
4-year	18.0%	8.2%	1.9%	5.1%
5-year	17.4%	7.2%	1.6%	4.7%
6-year	16.8%	6.7%	1.4%	4.6%
7-year	16.8%	6.1%	1.2%	4.4%
8-year	16.8%	5.7%	0.9%	4.1%
9-year	16.8%	5.6%	0.8%	3.9%
10-year	16.6%	5.3%	0.7%	3.6%

National Cancer Data Base

	AJCC Stage*				
	I	II	III	IV	TOTAL
Number of Cases	3210	2150	2802	7880	16042
	Percent Relative Survival**				
Years Following Diagnosis					
0	100	100	100	100	100
1	36	28	30	9	21
2	18	11	12	3	9
3	13	6	8	2	6
4	10	6	6	2	5
5	9	5	5	1	4

Рак поджелудочной железы:
5-ти летняя выживаемость в зависимости от вида

5-ти летняя выживаемость при раке поджелудочной железы

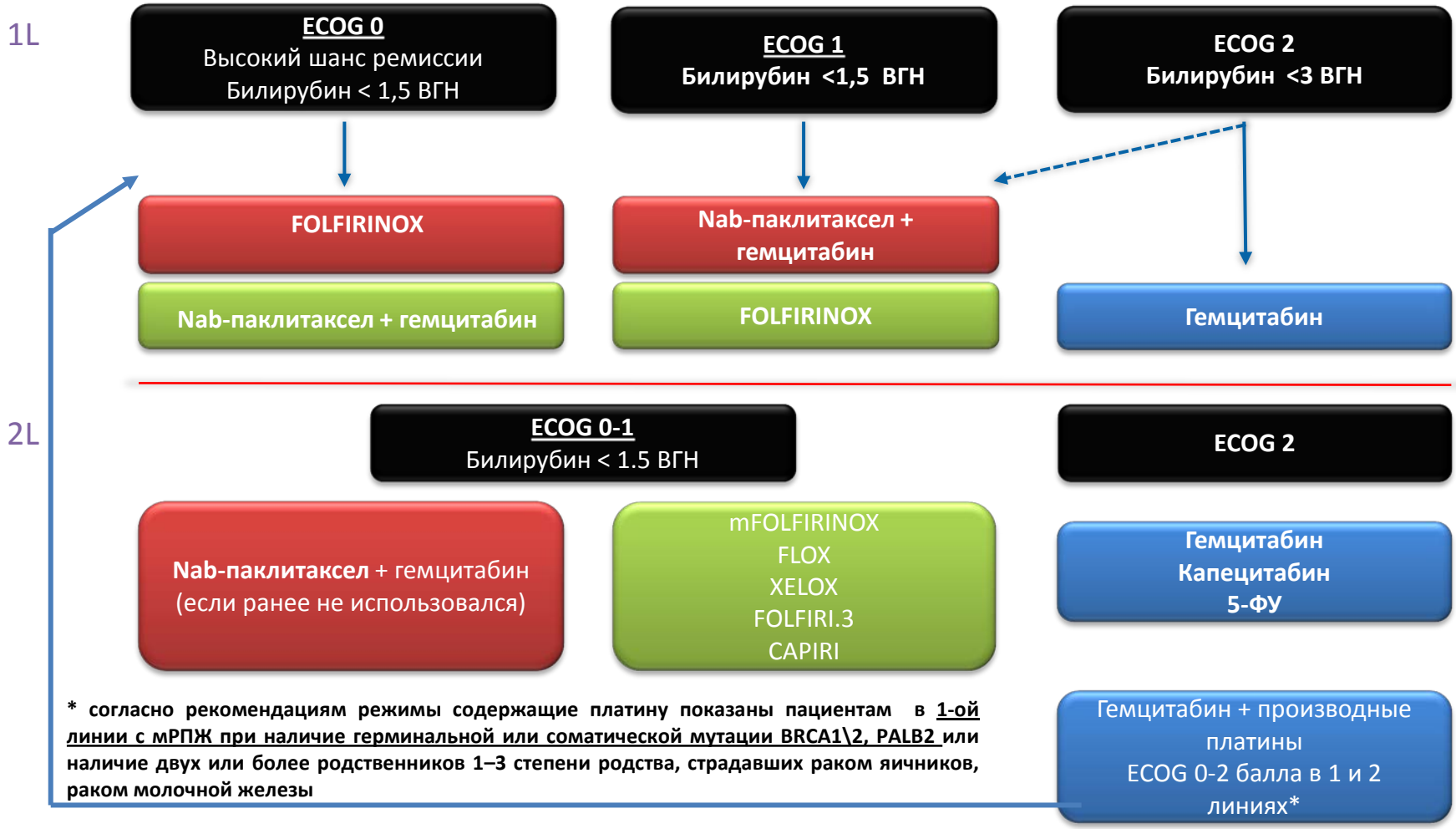


Экзокринный РПЖ
IA – 14 %
IB – 12 %
IIA – 7%
IIB – 5 %
III – 3 %
IV – 1 %

Эндокринный РПЖ
I – 61 %
II – 52%
III – 41 %
IV – 16 %

Fesinmeyer MD et al. Cancer Epidemiol Biomarkers Prev. 2005;14(7):1766-1773.
http://www.seer.cancer.gov -01.04.2017

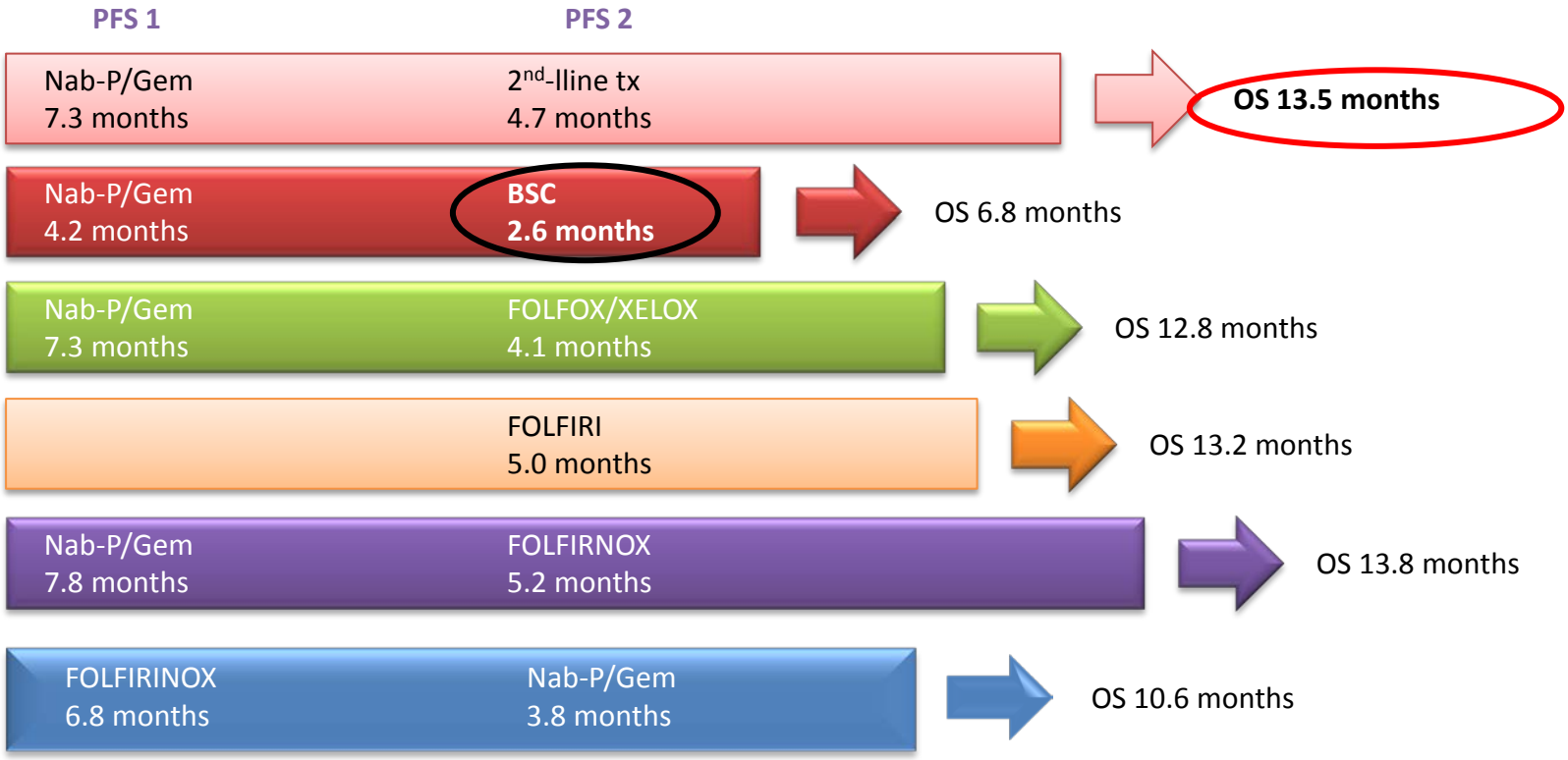
Алгоритм лечения пациентов с морфологически доказанным метастатическим раком поджелудочной железы



Покатаев и др.Практические рекомендации по лекарственному лечению злокачественных опухолей RUSSCO 2017; https://rosoncoweb.ru/standarts/RUSSCO/2017/recoms2017_25.pdf от 23.12.2017
Oettle H;Cancer Treat Rev;2014.http//dx.doi.org/10.1016/j.ctrv.2014.07.003

Эффективность химиотерапии II линии можно предсказать по эффективности химиотерапии I линии

	Эффект на II линии (коэф. корреляции Пирсона)	ВБП ≥4 месяца на II линии (коэф. корреляции Пирсона)
Эффект на I линии	0,298, p=0,06	0,531, p=0,003
ВБП ≥6 месяцев на II линии	0,321, p=0,002	0,560, p=0,031



Clin Oncol 34, 2016; suppl; abstr 4124;
Nab-paclitaxel and gemcitabine or FOLFIRINOX as first-line treatment in patients with unresectable adenocarcinoma of the pancreas: does sequence matter? Ursula M. Vogl at al

Dababou et al. Journal of Therapeutic Ultrasound (2017) 5:9
DOI 10.1186/s40349-017-0080-4

Journal of Therapeutic Ultrasound

RESEARCH Open Access

A meta-analysis of palliative treatment of pancreatic cancer with high intensity focused ultrasound

Susan Dababou[1*†], Cristina Marrocchio[1†], Jarrett Rosenberg[2], Rachelle Bitton[2], Kim Butts Pauly[2], Alessandro Napoli[3], Joo Ha Hwang[4] and Pejman Ghanouni[2]

Abstract

Background: Pancreatic adenocarcinoma is currently the fourth-leading cause of cancer-related death. Up to 60–90% of patients with advanced disease suffer cancer-related pain, severely impacting their quality of life. Current management involves primarily pharmacotherapy with opioid narcotics and celiac plexus neurolysis; unfortunately, both approaches offer transient relief and cause undesired side-effects. High intensity focused ultrasound (HIFU) is a non-invasive thermal ablation technique that has been used to treat pancreatic cancer. This meta-analysis aims to evaluate the role of HIFU in pain palliation of advanced unresectable pancreatic adenocarcinoma.

Methods: An electronic search was performed in PubMed Medline database up to the end of July 2016, for unresectable pancreatic cancer pain palliation with HIFU. Pertinent studies were identified through the PubMed search engine using the following keywords: HIFU, pancreas, pancreatic cancer, pain and palliation. Additional studies were included after manual search of the selected bibliographies. Pain palliation results reported in each study were analyzed using a logit-transformed random-effects model using the inverse variance method, with the DerSimonian-Laird estimator for τ^2, and Cochran's Q test for heterogeneity among studies. The I^2 was calculated to assess the percentage of the total variability in the different effect size estimates that can be attributed to heterogeneity among the true effects. A rank correlation test of funnel plot asymmetry was done to assess possible publication bias.

Results: The meta-analysis includes a total number of 23 studies with 865 patients, 729 with pancreatic cancer. The population enrolled ranges from 3 patients in the smallest series, up to 61 in the largest study. τ^2 (variance among studies) was 0.195, and I^2 (percentage of variation among studies) was 40% (95% CI: 1–64%); the Q test p-value was 0.026, indicating significant heterogeneity among studies. Among 639 patients treated with HIFU, 567 complained of pancreatic pain before the treatment and 459 patients experienced partial or complete pain relief after treatment. The random effects estimate of the proportion of patients with pain reduction was 0.81 (95% CI: 0.76–86).

(Continued on next page)

23 исследования

865 пациентов, 729 больных РПЖ
639 больных получали HIFU
567 пациентов до начала лечения испытывали болевой синдром
459 (80,9%) больных уменьшение или разрешение болевого синдрома после HIFU-терапии

* Correspondence: sdababou@gmail.com
†Equal contributors
[1]Medical Student, Sapienza University of Rome, School of Medicine, V.le Regina Elena, 324, 00180 Rome, Italy
Full list of author information is available at the end of the article

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Ther Clin Risk Manag. 2016 May 2;12:687-91. doi: 10.2147/TCRM.S90567. eCollection 2016.

High-intensity focused ultrasound therapy in combination with gemcitabine for unresectable pancreatic carcinoma.

Lv W[1], Yan T[1], Wang G[1], Zhao W[1], Zhang T[1], Zhou D[1].

Author information

1 Hepatobiliary Surgery Department, Second Artillery General Hospital, Xicheng District, Beijing, People's Republic of China.

Abstract

OBJECTIVE: To investigate the therapeutic effect and safety of high-intensity focused ultrasound (HIFU) therapy combined with gemcitabine in treating unresectable pancreatic carcinoma.

METHODS: The 45 patients suffering from pancreatic carcinoma were randomized into two groups. The patients in the experimental group (n=23) received HIFU in combination with gemcitabine and those in the control group (n=22) received gemcitabine alone. The effect and clinical benefit rates in the two groups were compared. The median survival time and 6-month and 12-month survival rates were calculated by Kaplan-Meier method and log-rank test.

RESULTS: The median survival time and 6-month survival rate were significantly higher in the experimental group than in the control group (8.91 months vs 5.53 months, 73.9% vs 40.9%, respectively P<0.05), but 12-month survival rate was not statistically different between the two groups (13.0% vs 4.5%, P>0.05). The clinical benefit rates in the experimental group and the control group were 69.6% and 36.3%, respectively (P<0.05). The pain remission rate in the experimental group was significantly higher than that in the control group (65.2% vs 31.8%, P<0.05).

CONCLUSION: HIFU in combination with gemcitabine is better than gemcitabine alone. This combinatorial therapy may become a better and effective treatment for unresectable pancreatic carcinoma.

KEYWORDS: gemcitabine; high-intensity focused ultrasound therapy; pancreatic carcinoma treatment

PMID: 27194912 PMCID: PMC4859417 DOI: 10.2147/TCRM.S90567

Free PMC Article

45 пациентов нерезектабельный РПЖ
23 пациента HIFU+Gem
22 пациента Gem
мОВ в течение 6 мес 8,96 vs 5,53
клиническая польза 69,6% vs 36,3%
ремиссия боли 65,2% vs 31,8%

Cancer Manag Res. 2018; 10: 4439–4446.
Published online 2018 Oct 9. doi: 10.2147/CMAR.S173740

PMCID: PMC6188211
PMID: 30349376

Response of patients with locally advanced pancreatic adenocarcinoma to high-intensity focused ultrasound treatment: a single-center, prospective, case series in China

Yongshuo Ji,[1] Yu Zhang,[1] Jungiu Zhu,[1] Linglin Zhu,[1] Yanfei Zhu,[1] Kaimeng Hu,[2] and Hong Zhao[1]

Au

Patients and methods

Eighty-seven cases with unresectable LAPC from January 2014 to December 2016 were finally recruited according to the inclusion criteria. The primary end point of our study was OS of all the cases, and the secondary end points included 6-month and 12-month survival rate, tumor response rate, carbohydrate antigen (CA) 19-9 response rate, VAS, quality of life, and safety.

Results

All the 87 patients received HIFU ablation successfully, and were included in the efficacy and safety analysis. With a median follow-up of 16 months, median OS was estimated to be 12.2 months, with 95 % CI of 11.1–12.7 months. The 6-month and 12-month survival rates were 94.25% (95% CI =86.74–97.57) and 50.85% (95% CI =38.17–62.21), respectively. Multivariate analysis revealed that patients with VAS <4, Karnofsky performance status ≥80, and tumor size <3 cm have a significant improvement in their OS (adjusted HR [aHR] =0.26 [95% CI =0.12–0.57], P=0.001; aHR =0.34 [95% CI =0.17–0.68], P=0.02; and aHR =0.39 [95% CI =0.20–0.78], P=0.007; respectively). Tumor responses were observed in 32 (36.8%) of 87 patients and CA 19-9 response rate was 56.2%. Global health status, physical function, emotional function, and cognitive function of patients were significantly improved after HIFU treatment, and symptoms of fatigue and pain were significantly reduced. A total of 28.7% (25/87) of patients reported adverse events (AEs), mainly including fatigue (14/87), abdominal pain (7/87), fever (7/87), nausea (5/87), and rash (4/87). No severe AEs and HIFU-related deaths were reported.

Conclusion

HIFU ablation might be a potentially effective and safe therapeutic option for the patients with

32 пациента нерезектабельный РПЖ
III ст – 23 пац., IV ст – 9 пац.
HIFU + XT с включением гемцитабина
Клинический ответ в течение 8 недель после HIFU – 82%
CR – 8 пациентов (25%)
мОВ – 12,5 мес (6 мес – 2,5 лет)
Осложнения: панкреатит, ожог кожи

Conference Paper

Complete Responses after Hyperthermic Ablation by Ultrasound Guided High Intensity Focused Ultrasound Plus Systemic Chemotherapy for Locally Advanced Pancreatic Cancer

Joan Vidal-Jove,[1] Marta Garcia-Bernal,[2] Eloi Pericle,[1] and Manuel Alvarez del Castillo[3]

[1]Surgical Oncology HIFU Unit, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain
[2]Pediatric Department, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain
[3]Medical Direction Department, Hospital Universitari Mutua Terrassa (HUMT), Placa Dr. Robert 5, 08221 Terrassa, Barcelona, Spain

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Views	652
Citations	0
ePub	22
PDF	219

Abstract

We describe results in unresectable pancreatic tumors treated with USgHIFU hyperthermia ablation plus adjuvant chemotherapy. *Materials and Methods*. Thirty two cases of nonresectable pancreatic tumors were treated from March 2010 to March 2012, and all of them underwent systemic chemotherapy. Clinical responses (thermal ablation achieved) were measured by image techniques. There were 23 stage III cases and 9 stage IV cases. Complications were also analyzed. *Results*. Clinical responses (ablation obtained) were 82% in all cases, sustained at 8 weeks of the procedure. We obtained 8 complete responses (25%) at the end of the combined treatment, 7 from stage III patients and 1 from stage IV. Major complications included (1) severe pancreatitis with GI bleeding and (2) skin burning grade III that required plastic surgery. No deaths were registered. Median survival was 12.5 month (6 months–2.5 year). *Conclusion*. HIFU plus SC is a potentially effective and safe modality for the treatment of unresectable pancreatic cancer.

ДИЗАЙН ИССЛЕДОВАНИЯ: ОЦЕНКА ЭФФЕКТИВНОСТИ КОМБИНАЦИИ МХТ И HIFU-ТЕРАПИИ У ПАЦИЕНТОВ СТАРШЕЙ ВОЗРАСТНОЙ ГРУППЫ И ОСЛАБЛЕННЫХ ПАЦИЕНТОВ С НЕРЕЗЕКТАБЕЛЬНЫМ РПЖ

Нерезектабельный или метастатический РПЖ (не более 3 mts в печени до 3 см)

Невозможность хирургического лечения, комбинировнаной ХТ
- ECOG 1-2
- Коморбидность

Гистологическая или цитологическая верификация (аденокарцинома)

Гемцитабин 1000 мг/2 в 1, 8, 15 дни каждые 4 недели
Лечение до прогрессирования либо неприемлемой токсичности

6-8 сеансов HIFU-терапии 2-5 и 7-10 дни курса между введениями мощность 400-600 ВТ

прогрессирование

При сохранении Общего удовлетворительного статуса Пациента смена варианта ХТ (капецитабин, Иринотекан с продолжением HIFU-терапии

Основная конечная точка: ОВ
Вторичная конечная точка: БРВ, частота объективного ответа, безопасность

Характеристики пациентов

Количество пациентов	**30 больных – 23 женщины и 7 мужчин**
Возраст пациентов	Средний возраст 69,5 лет (от 54 до 81 года, 50% больных старше 70 лет)
Стадия: II А ст., cT3N0M0 II В ст., cT1-3N1M0 III ст., cT1-3N2M0 cT4NлюбаяM0 **cTлюбаяNлюбаяM1**	 6 пациентов 10 пациентов 5 пациентов 9 пациентов (у 8 больных cT4No-1M1)
Сопутствующая патология: Кардиальная СД ДН	 28 пациентов (93%) 8 пациентов (26,6%) 5 пациентов (16,6%) 100% комбинированная
Болевой синдром	24 пациента (80%)
Потеря массы тела более 10%	24 пациента (80%)
1 линия ХТ 2 и более линии ХТ	17 5

ПРЕДВАРИТЕЛЬНЫЕ РЕЗУЛЬТАТЫ

мВДП - 11 месяцев (прогрессия зарегистрирована у 22 больных)
мОВ - 15 мес (умерло 17 пациентов)

ПР – 1 пациентка
СП – 5 пациентов

Контроль болевого синдрома:
Отказ от обезболивания – 10 (41,6%) больных
Снижение болевого синдрома - 4 (16,6%) пациента

Осложнения:
Ожог кожи – 4 пациента

ЗАКЛЮЧЕНИЕ

1. Комбинация HIFU-терапии и химиотерапии на основе гемцитабина потенциально эффективный и безопасный метод лечения у пациентов нерезектабельны РПЖ. В том числе и у больных старшей возрастной группы, ослабленных больных и пациентов с выраженной сопутствующей патологией.

2. Проведение HIFU-терапии в комбинации с ХТ улучшает качество жизни пациентов с нерезектабельным РПЖ за счет снижения интенсивности болевого синдрома и улучшения общего состояние пациентов.

3. Требуется дальнейшая оценка возможностей применения HIFU-терапии с более интенсивными режимами ХТ у больных с нерезектабельным РПЖ или рецидивом заболевания.

Спасибо за внимание