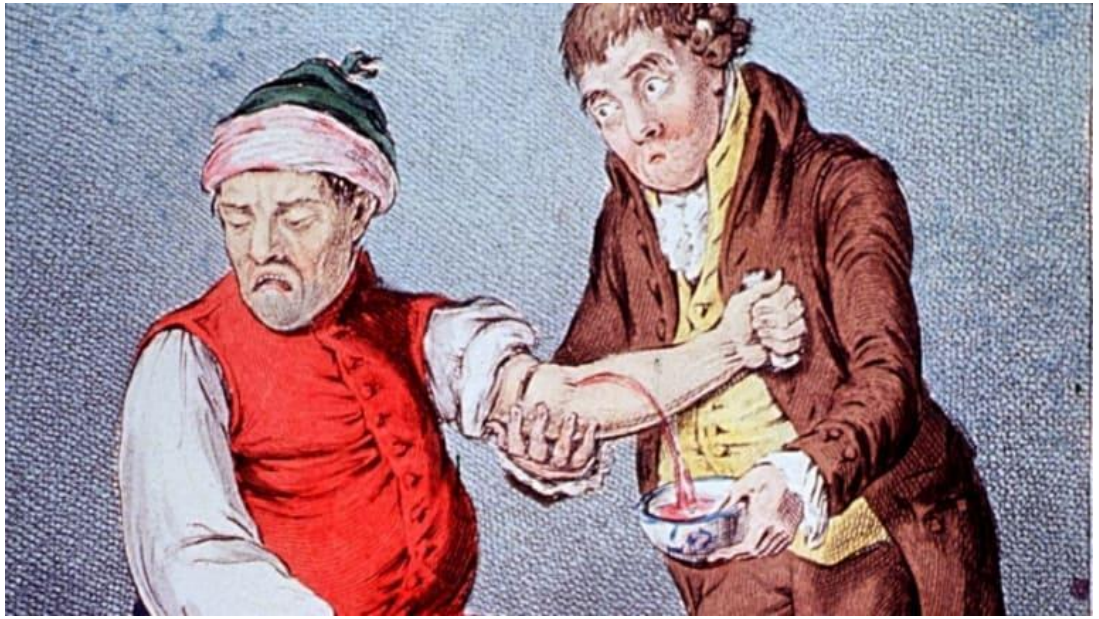
Доказательная медицна



- Начиная с 10 века до нашей эры кровопусканием лечились многие заболевания от лихорадки до психических расстройств.
- Гиппократ и Гален рекомендовали кровопускания
- И все были счастливы, пока н

Лечение пневмонии кровопусканием

N=77	Группа кровопускания	Контроль	Разница
Смертность	44%	25%	-19%

Вывод: кровопускание оказалось менее эффективным метод лечения пневмонии, чем ожидалось.

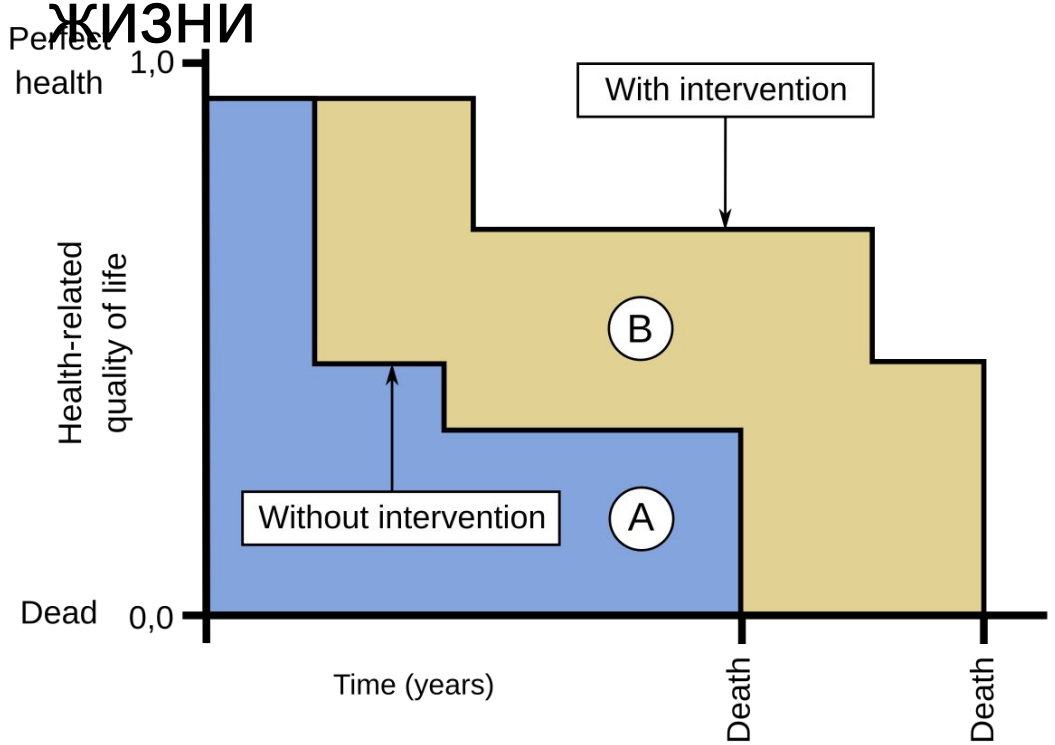
- С тех пор многое изменилось
- Но в чем-то мы верны традициям

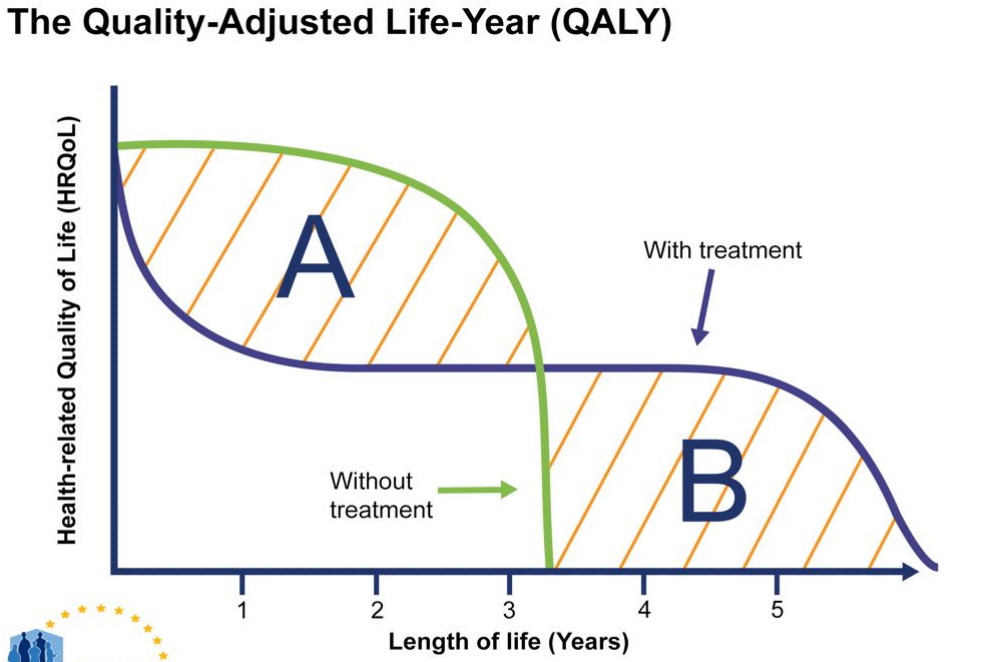
Как доказать, что вмешательство А лучше вмешательства В или отсутсвия вмешательства?

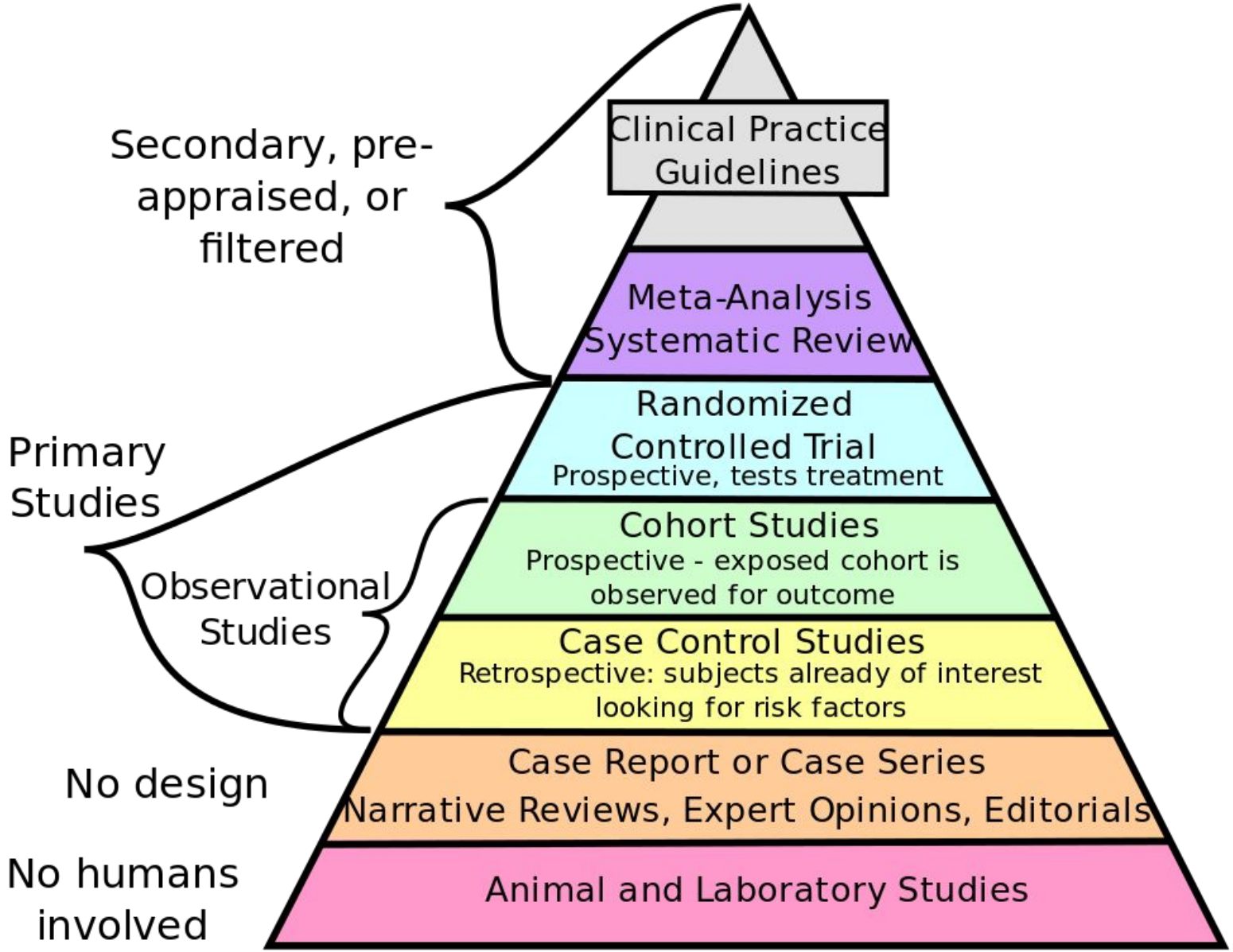
- 3 цели в медицине:
- Вылечить (cure) (частота излечения / смертность);
- Продлить жизнь (treatment) (средняя продолжительность жизни);
- Улучшить качество жизни (шкалы оценки качества жизни)
  - Боль;
  - Слабость
  - Тошнота, рвота;
  - Финансовая токсичность;
  - Необходимость пропускать работу;
  - Время, потраченное на лечение;

Онкология: качество жизни в обмена на продолжительность жизни?

- Quality-adjusted life year
- Качество жизни более субъективно и многогранно и очень немногие исследования в онкологии оценивают качество жизни






Secondary, pre-appraised, or filtered
Clinical Practice Guidelines
Meta-Analysis
Systematic Review
Primary Studies
Randomized Controlled Trial
Prospective, tests treatment
Observational Studies
Cohort Studies
Prospective - exposed cohort is observed for outcome
Case Control Studies
Retrospective: subjects already of interest looking for risk factors
No design
Case Report or Case Series
Narrative Reviews, Expert Opinions, Editorials
No humans involved
Animal and Laboratory Studies

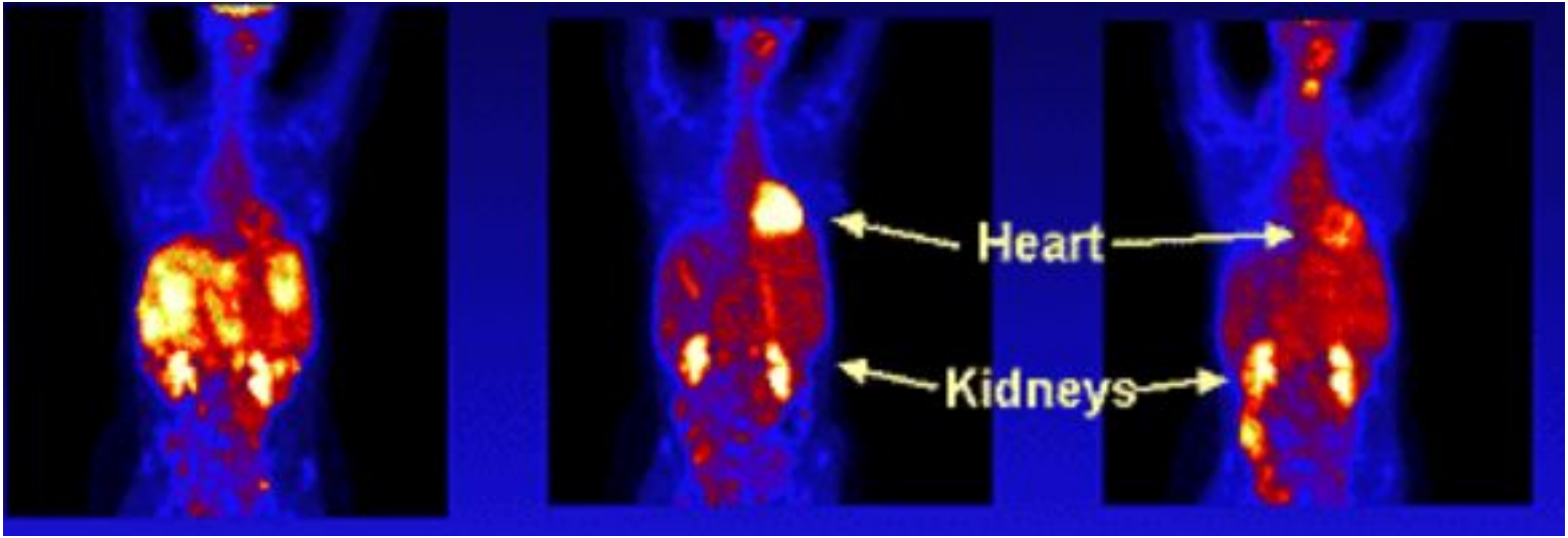
Мнение эксперта

Кровопускание лечит от всех недугов

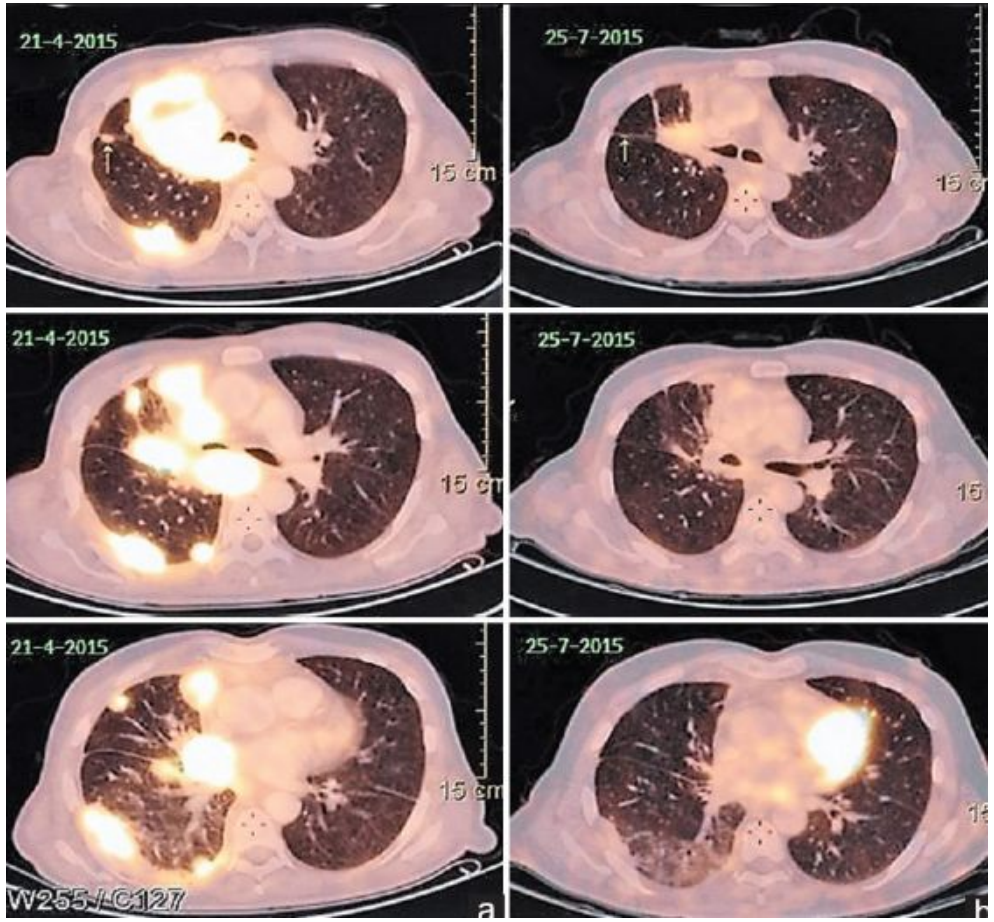
При кровотечении необходимо наложить жгут

Медицина ≠

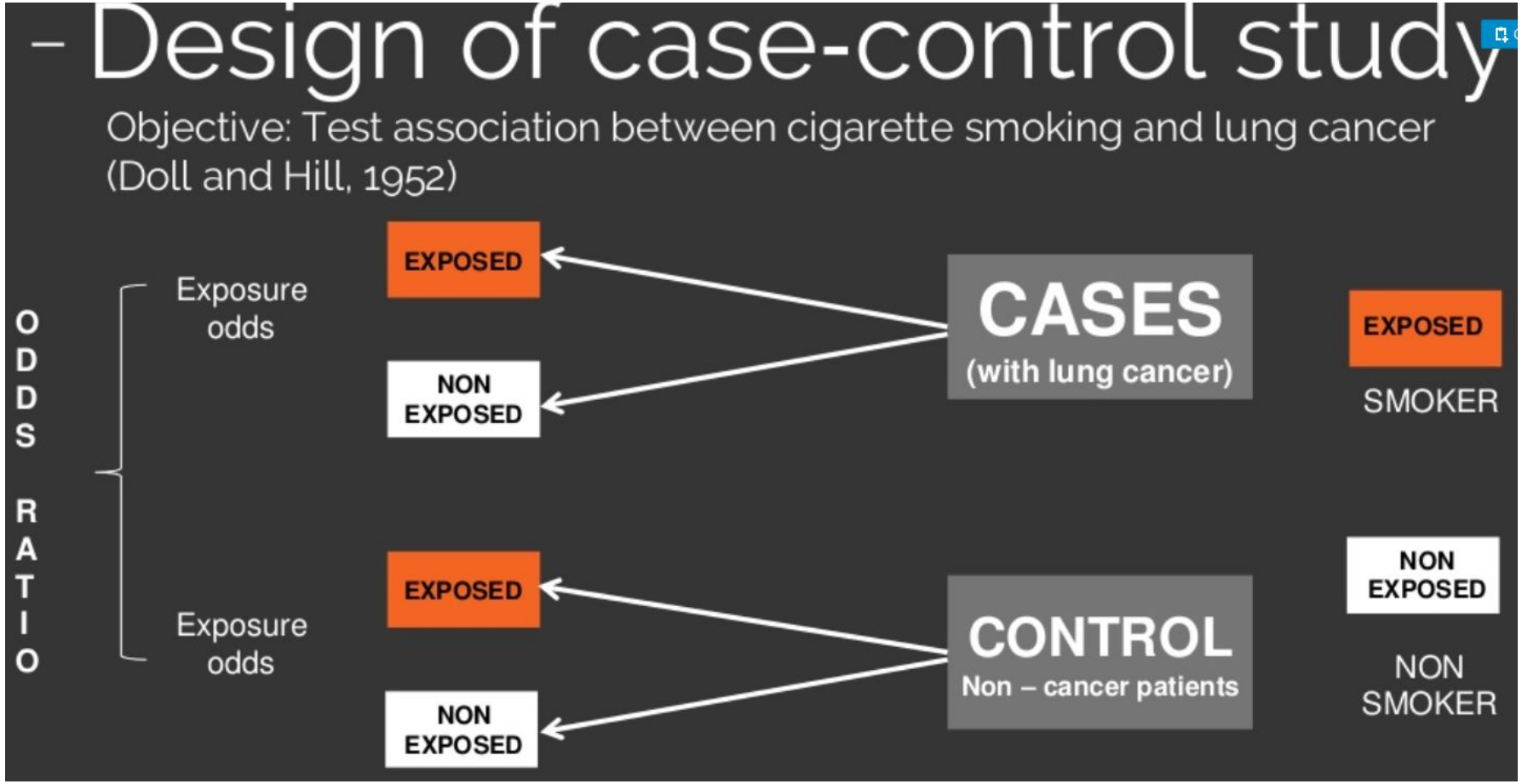
Case report – клинический случай



Case-series – серия клинических случаев



Case-control



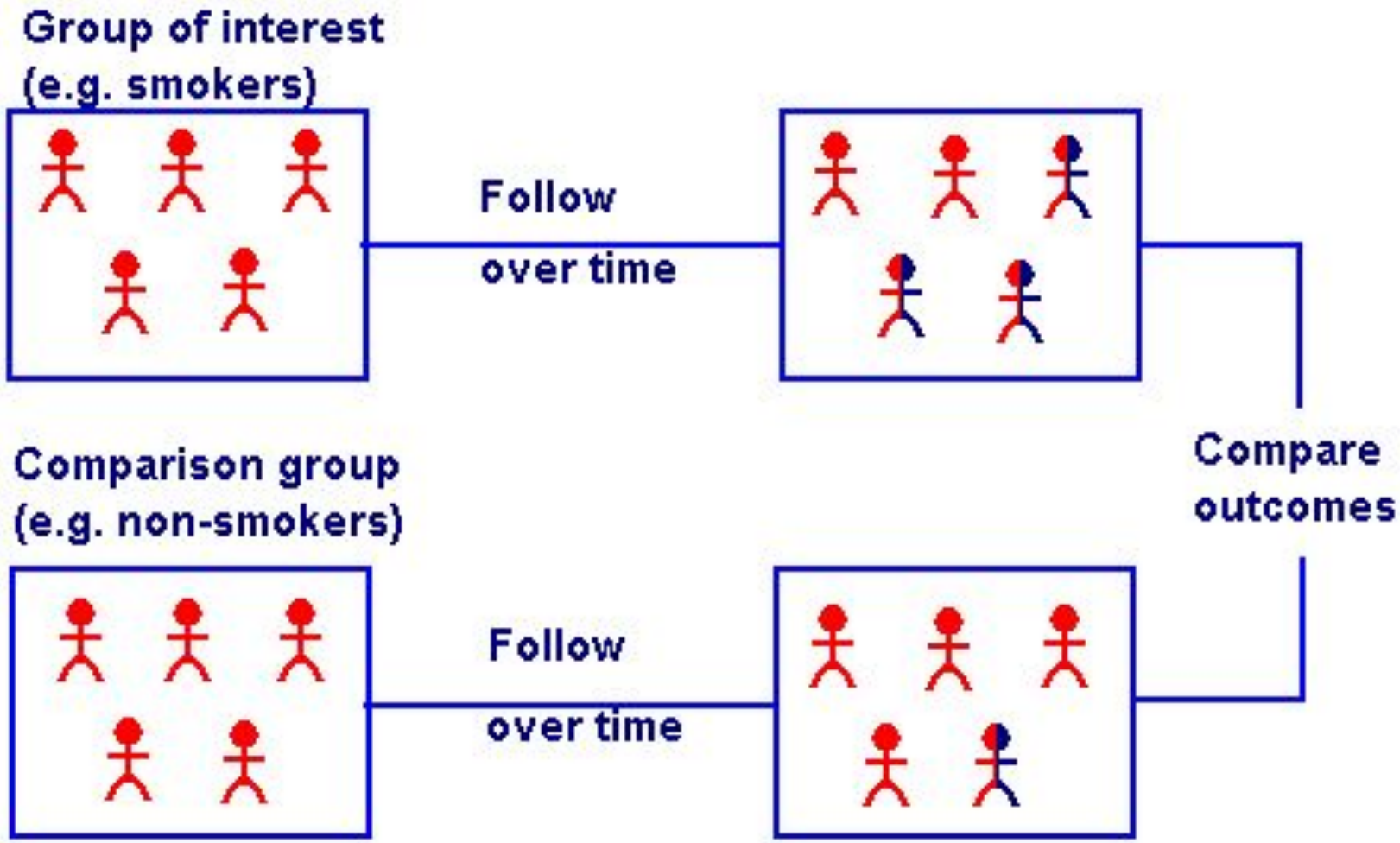
Case-control

5. In the 1950s, Doll and Hill performed a classic study of the causes of lung cancer in men. Although it was not called a case-control study at the time, it was one of the first uses of this study design. Briefly, the investigators identified men with biopsy confirmed lung cancer as cases, and patients with diseases other than cancer as controls. The data are tabulated in the table below.

	Lung Cancer Cases	Controls
Cigarette smoking	647	622
No smoking	2	27

Using these data, calculate the odds ratio. Show all of your work for full credit. What conclusions would you draw from this case-control study?

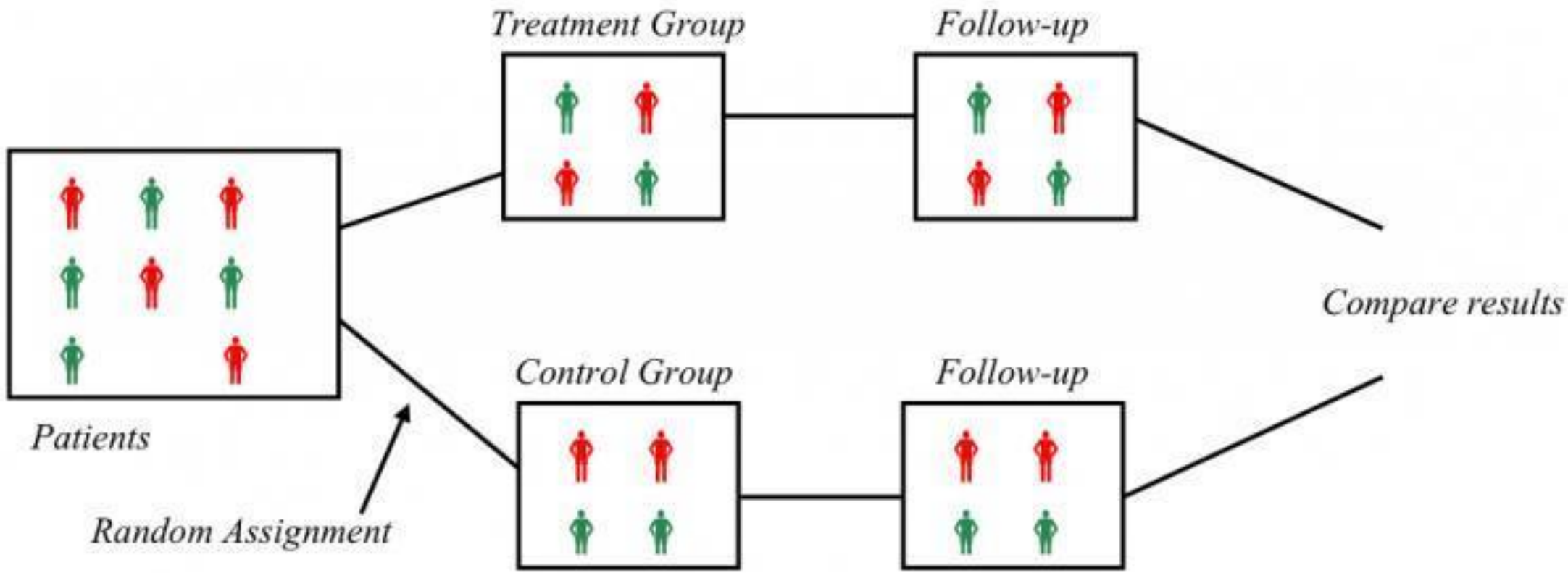
Когортное исследвание



Недостатки case-control и когортного исследования?

- Группы могут быть несравнимы
- Что если большинство курящих в исследовании также работали / работают на вредных производствах?
- Что если все болезни от нервов и курение вторично?

Двойное слепое проспективное рандомизированное исследование

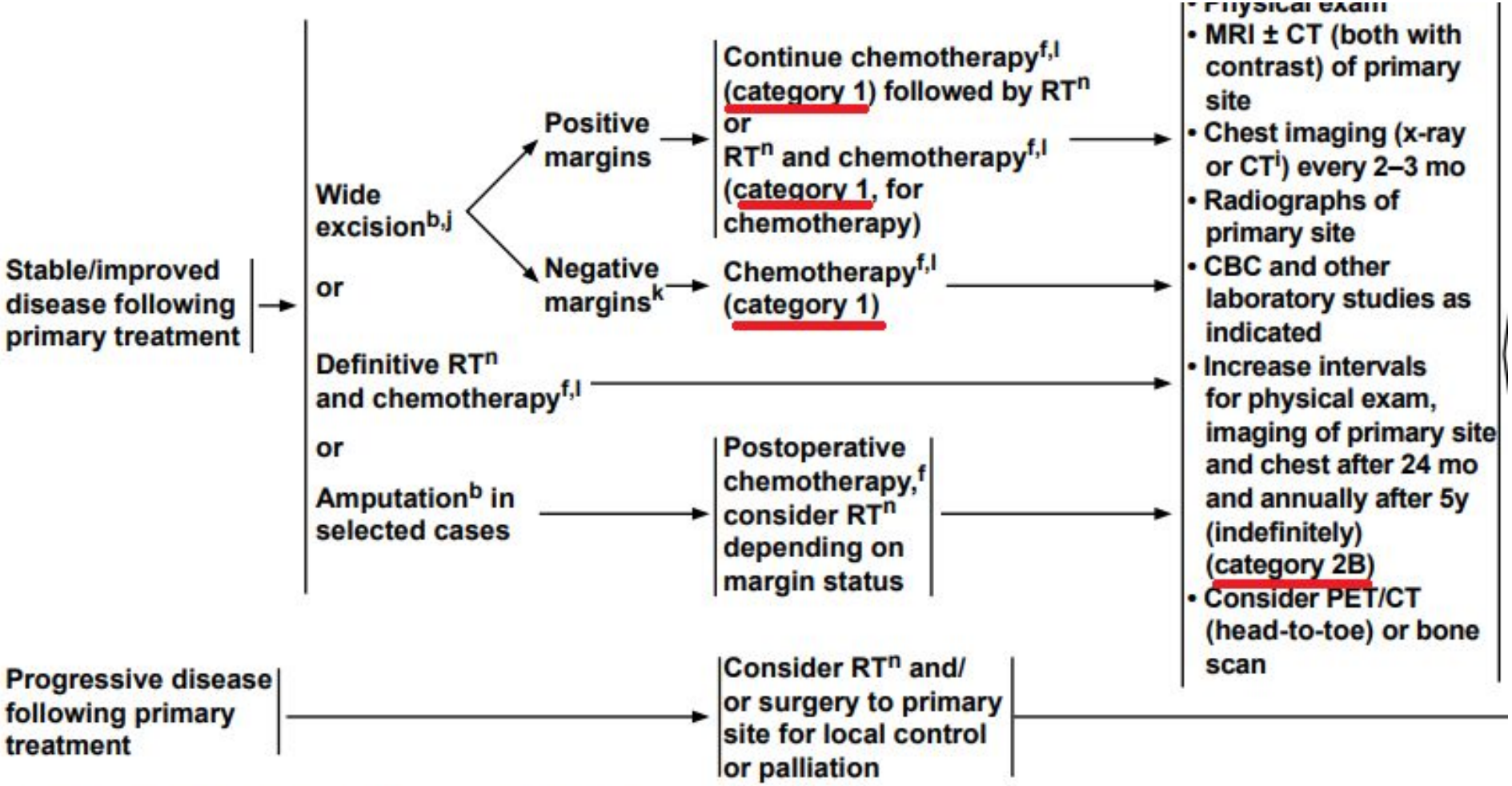


Фазы современного клинического исследования

- Преклиническая. Лекарственное средство тестируется на животных, клеточных культурах и т.д.
- Фаза I. Тестирование ЛС на здоровых добровольцах для оценки токсичности;
- Фаза II. Тестирование ЛС на пациентах для ориентировочной оценки токсичности и эффективности;
- Фаза III. Двойное слепое рандомизированное плацебо-контролируемое исследование
- Заявка на регистрацию в FDA
- Фаза IV. Постмаркетинговое наблюдение.

Уровни доказательности

- Категория I. Имеется хотя бы 1 рандомизированное исследование с надлежащим дизайном
- Категория IIA. Имеются когортные и case-control исследования с надлежащим дизайном
- Категория IIB. Имеются case-series
- Категория III. Мнение экспертов, клинические случаи.



[b] See Principles of Bone Cancer Management (BONE-A).
[f] See Bone Cancer Systemic Therapy Agents (BONE-B).
[i] Chest CT with or without contrast as clinically indicated.
[j] Consider preoperative RT for marginally resectable lesions.
[k] RT may be considered for close margins.
[l] There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule use
[m] For late relapse, consider re-treatment with previously effective regimen.
[n] See Principles of Radiation Therapy (BONE-C).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encourag

Overview

In 2016, an estimated 76,380 patients will be diagnosed with and about 10,130 patients will die of melanoma in the United States.[1] However, these figures for new cases may represent a substantial underestimate, as many superficial and in situ melanomas treated in the outpatient setting are not reported. The incidence of melanoma continues to increase dramatically, at an overall rate of 33% for men and 23% women from 2002 to 2006.[2] Melanoma is increasing in men more rapidly than any other malignancy, and in women more rapidly than any other malignancy except lung cancer.[3] Based on data from 2009 to 2011, the lifetime risk of developing cutaneous melanoma is 1 in 34 for women and 1 in 53 for men.[1] The median age at diagnosis is 59 years. On average, an individual loses 20.4 years of potential life as a result of melanoma mortality compared to 16.6 years for all malignancies.[4]

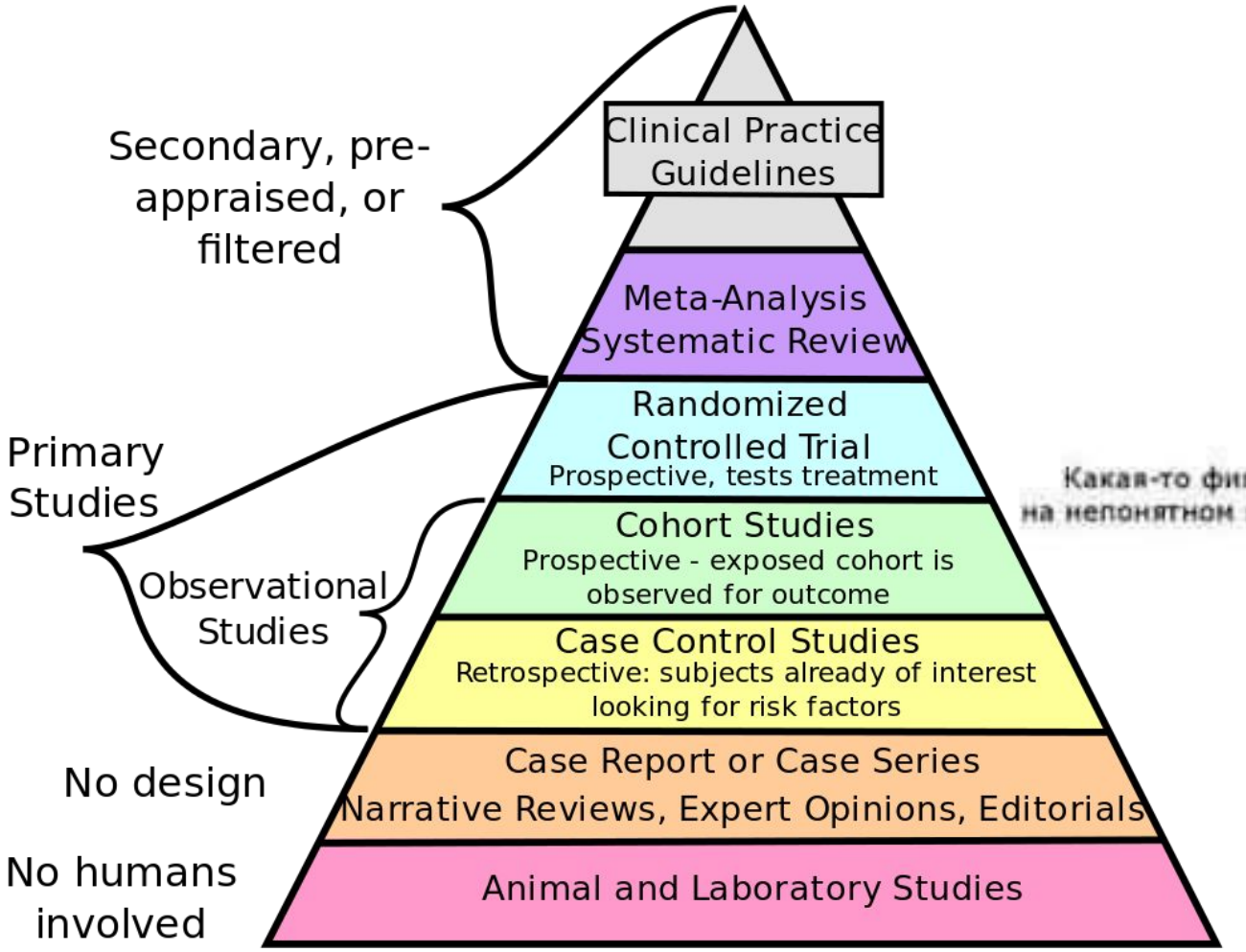
Risk factors for melanoma include skin type, personal history of prior melanoma, multiple clinically atypical moles or dysplastic nevi, a positive family history of melanoma,[5-8] and rarely, inherited genetic mutations. Genetic counseling could be considered for individuals with a strong family history of invasive melanoma with or without pancreatic cancer. In addition to genetic factors, environmental factors including excess sun exposure and UV-based artificial tanning contribute to the development of melanoma.[9-11] The interaction between genetic susceptibility and environmental exposure is illustrated in individuals with an inability to tan and fair skin that sunburns easily who have a greater risk of developing melanoma.[12,13] However, melanoma can occur in any ethnic group and also in areas of the body without substantial sun exposure.

84% of patients with melanoma initially present with localized disease, 9% with regional disease, and 4% with distant metastatic disease.[15] In general, the prognosis is excellent for patients who present with localized disease and primary tumors 1.0 mm or less in thickness, with 5-year survival achieved in more than 90% of patients.[14] For patients with localized melanomas more than 1.0 mm in thickness, survival rates range from 50% to 90%, depending on tumor thickness, ulceration, and mitotic rate.[14] The likelihood of regional nodal involvement increases with increasing tumor thickness, as well as the presence of ulceration and mitotic rate.[16-19] When regional nodes are involved, survival rates are roughly halved. However, within stage III, 5-year survival rates range from 20% to 70%, depending primarily on the nodal tumor burden.[14] Historically, long-term survival in patients with distant metastatic melanoma, taken as a whole, has been less than 10%. However, even within stage IV, some patients have a more indolent clinical course that is biologically quite distinct from most patients with advanced disease. Furthermore the impact of emerging effective systemic therapies on the survival of patients with stage IV melanoma, either at presentation or recurrence, has made long-term remission possible for a larger proportion of patients.

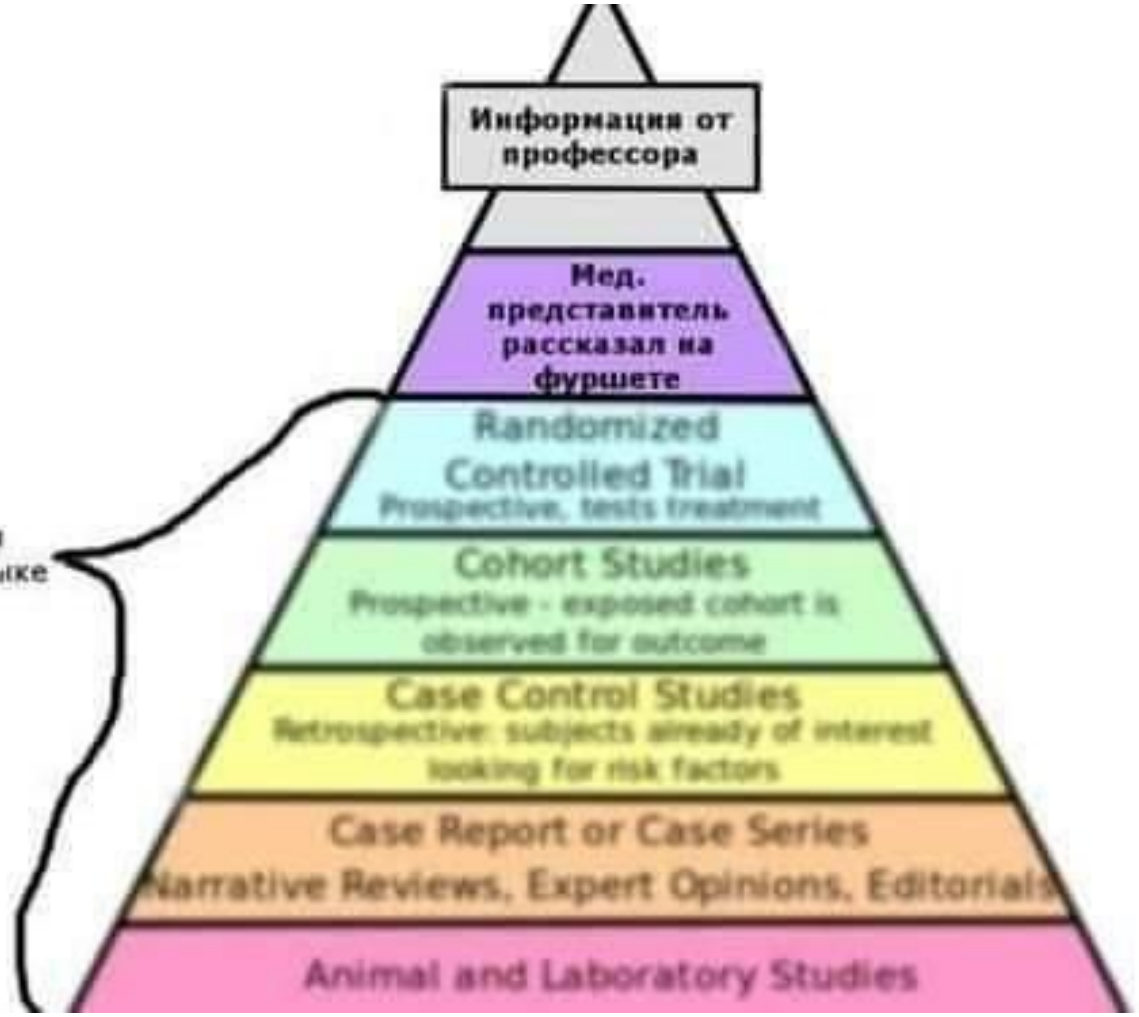
There is increasing appreciation of the variations in specific genetic alterations among distinct clinical subtypes of melanoma. The currently described clinical subtypes of cutaneous melanoma are: non-chronic sun damage (non-CSD): melanomas on skin without chronic sun-induced damage; CSD: melanomas on skin with chronic sun-induced damage signified by the presence of marked solar elastosis; and acral: melanomas on the soles, palms, or sub-ungual sites. Melanocytes exist

Доказательная медицина

Ожидание



Реальность



Частые уловки в дизайне исследования

- Сравнение с нестандартной терапией
- Проведение большого количества исследований с небольшим изменением дизайна
- Непубликация отрицательных результатов;
- При получении отрицательных результатов – поиск «факторов риска» при которых препарат все-таки эффективен
- Не те цели и задачи в дизайне исследования (primary end points) – например, период без прогрессирования и частота ответов вместо общей выживаемости;
- Комбинация одной терапии с другой в условиях паллиативной терапии

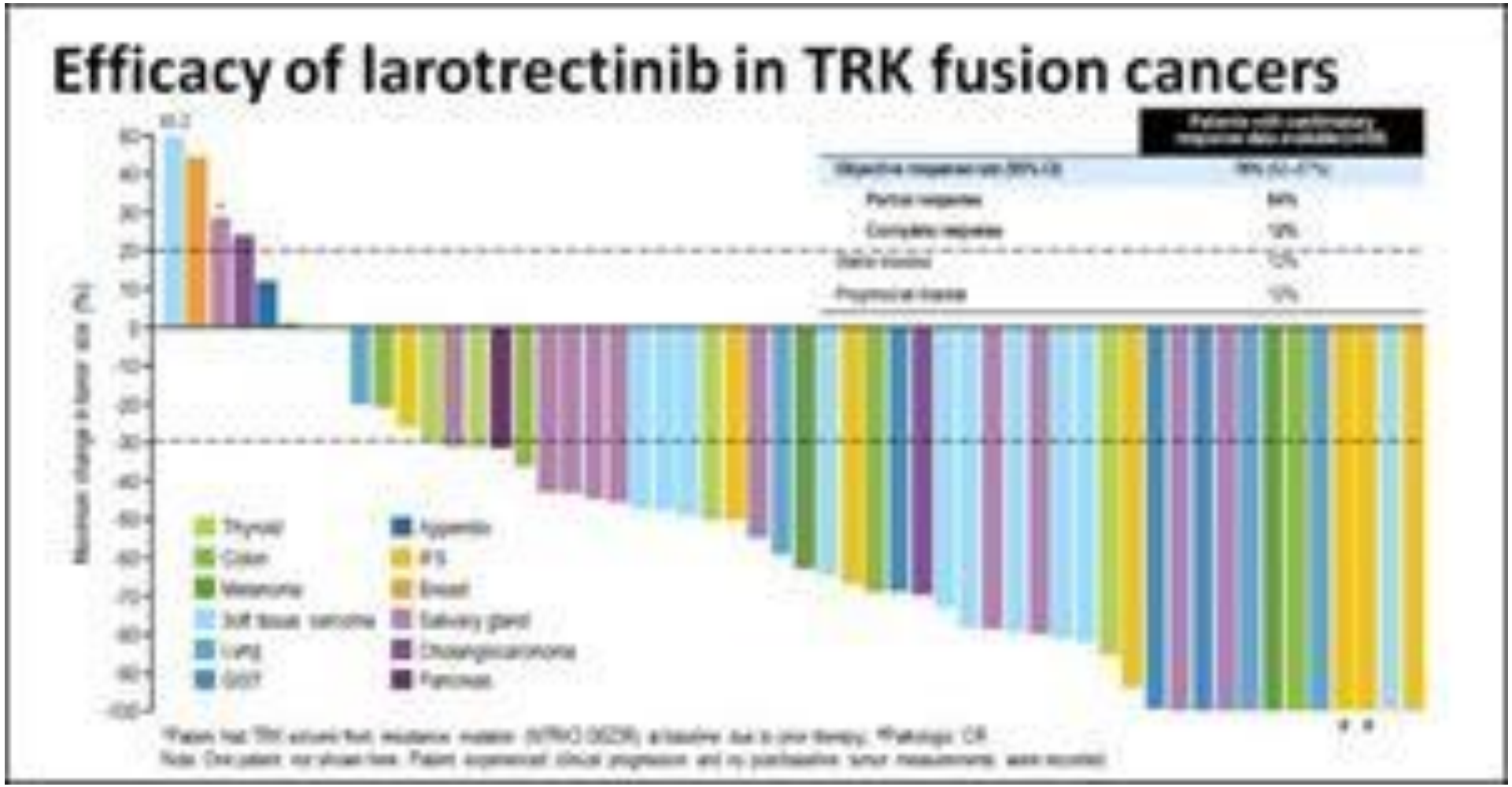
Может ли врач оценить качество клинического исследования?

- Может и долежн
- Но нужны контролирующие органы

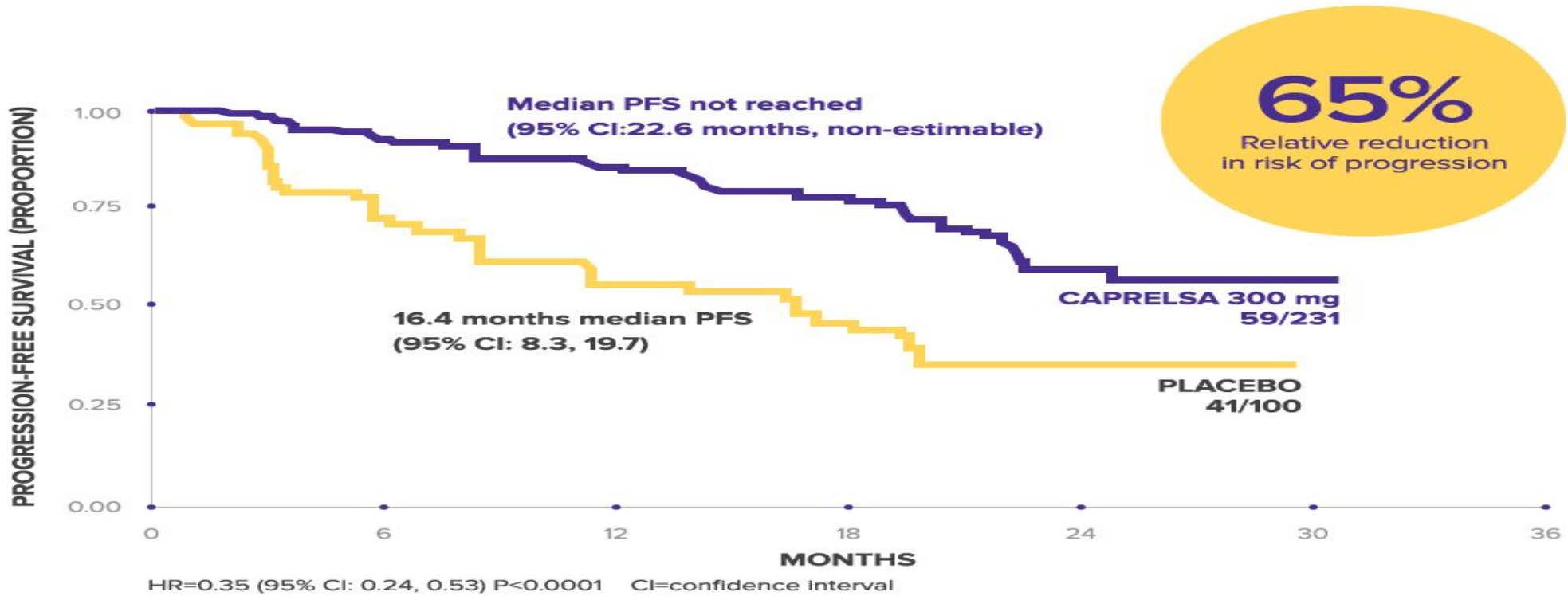
Где публигуются нулевые и негативные результаты исслезований?

- Журнал «Медицина Эфиопии»
- Вестник СПбГУ
- На сайте ClinicalTrials.gov

Частота ответов (PFS)



Медиана без прогрессирования



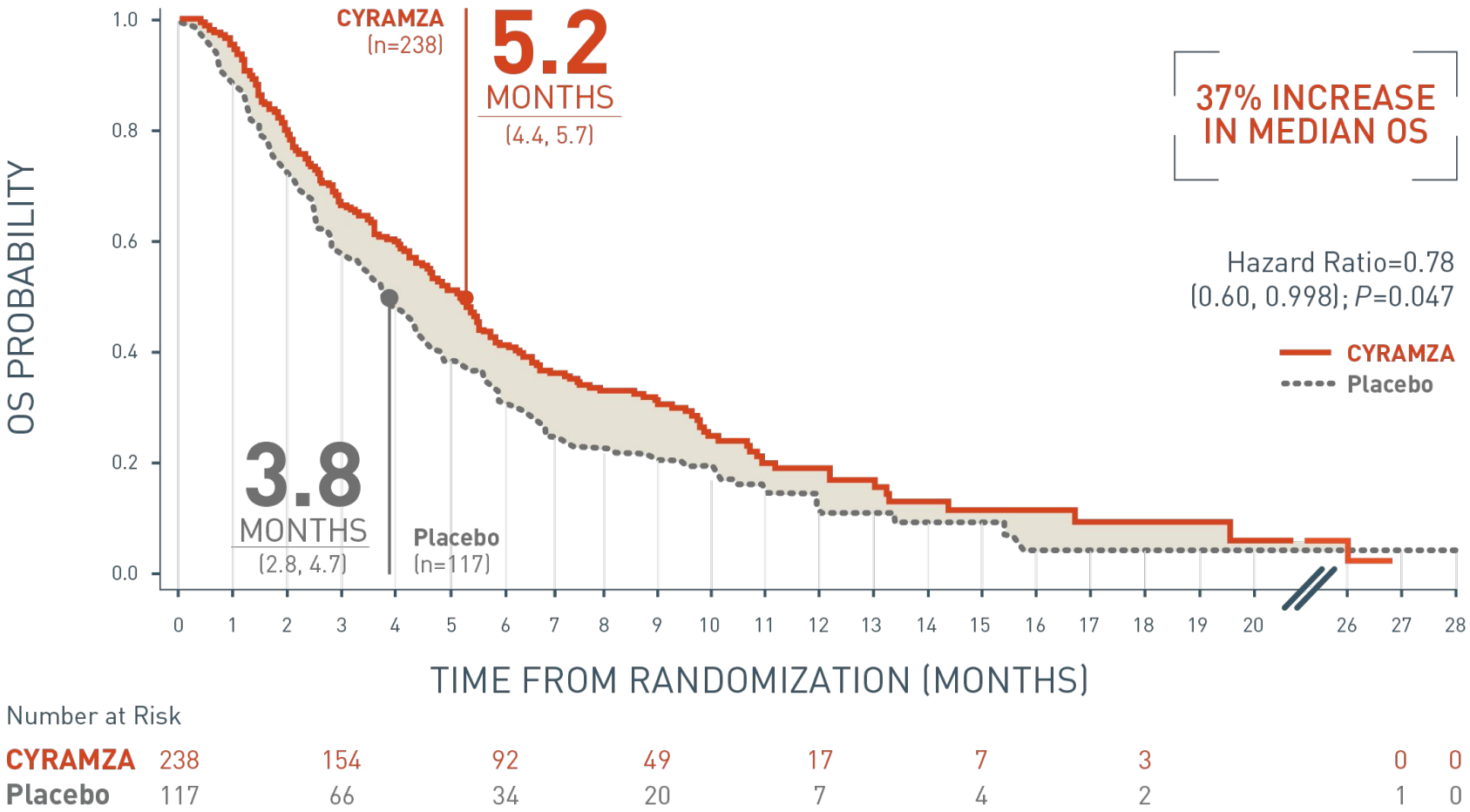
HR=0.35 (95% CI: 0.24, 0.53) P<0.0001 CI=confidence interval

NUMBER AT RISK

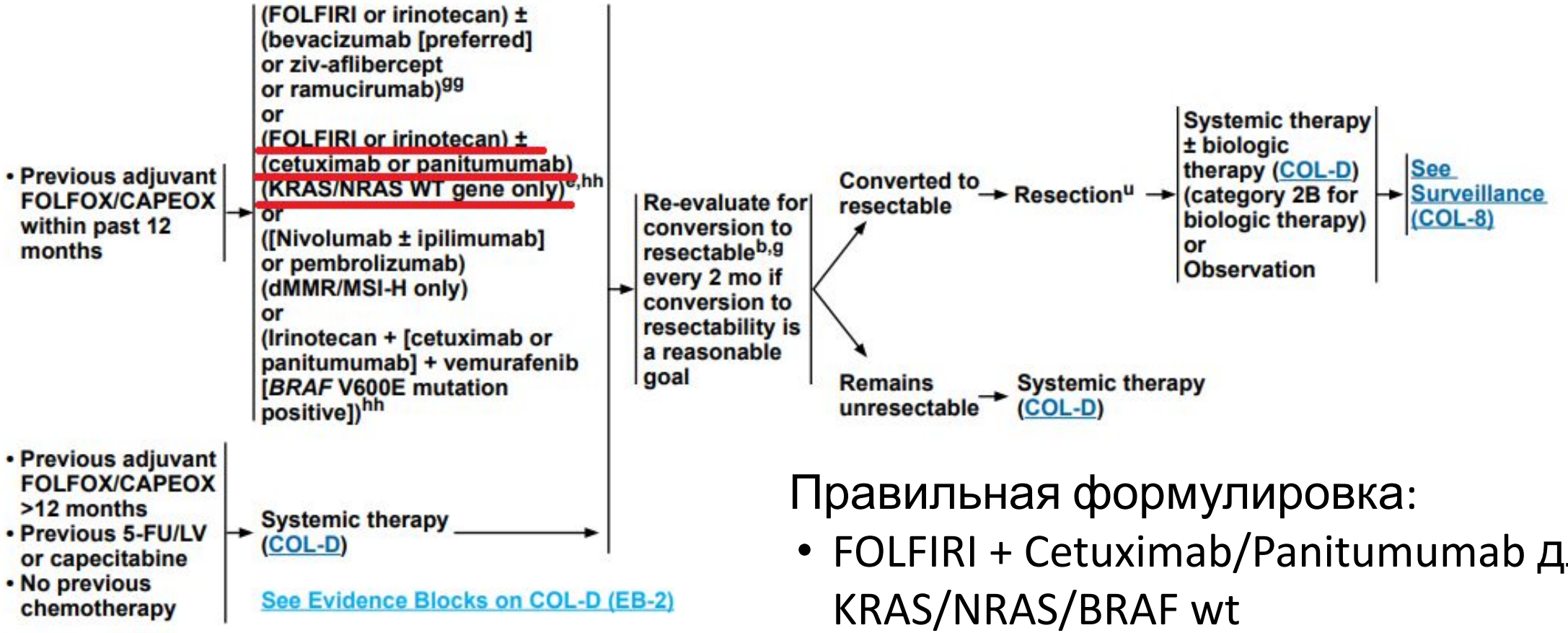
231	173	145	118	33	1	0	CAPRELSA 300 mg
100	47	30	24	6	0	0	Placebo

CI=confidence interval.

Общая выживаемость (OS)



Гайдлайны и Фарм. Компании



Правильная формулировка:

- FOLFIRI + Cetuximab/Panitumumab для KRAS/NRAS/BRAF wt
- Cetuximab + Vemurafenib для BRAF V600E

[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B 4 of 5) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.
[g] See Principles of Surgery (COL-C 2 of 3).
[u] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[gg] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[hh] *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor.

ADJUVANT ENDOCRINE THERAPY

Должно быть

Premenopausal[1] at diagnosis →

- **Tamoxifen[4] for 5 y (category 1)**
- **Aromatase inhibitor[3] for 5 y + ovarian suppression or ablation (category 1)[2]**