Различные конечные точки в онкологических исследованиях и их взаимосвязь

Докладчик: Анастасия Божко
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METHODS OF CANCER THERAPY

LOCAL

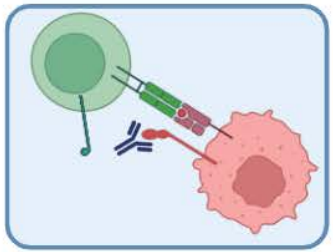
Surgery

Radiation

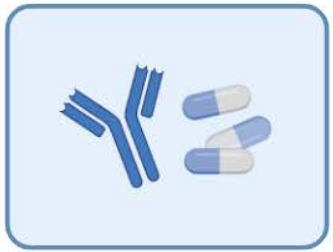
SYSTEMIC

Chemotherapy

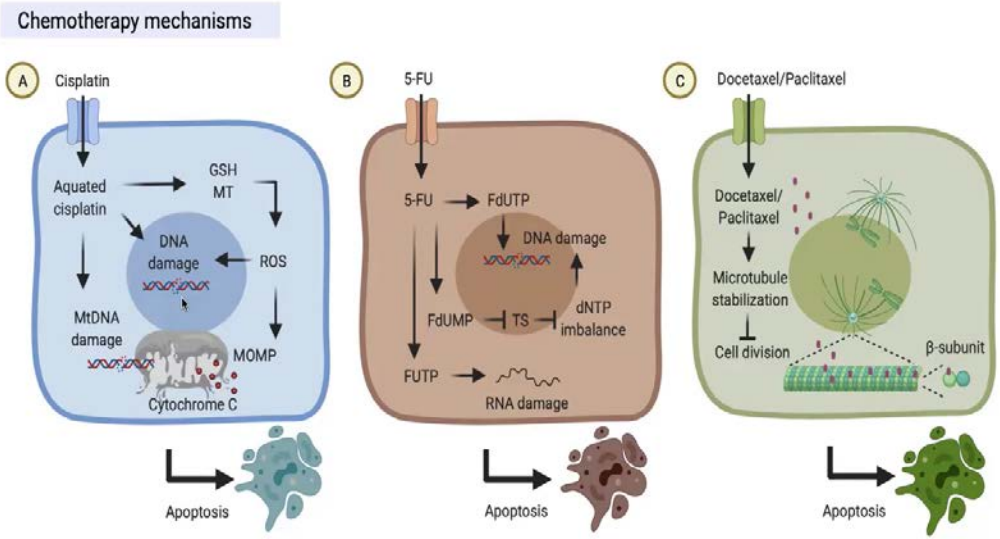
Immuno therapy



Targeted therapy



Источник: графический конструктор Biorender.com



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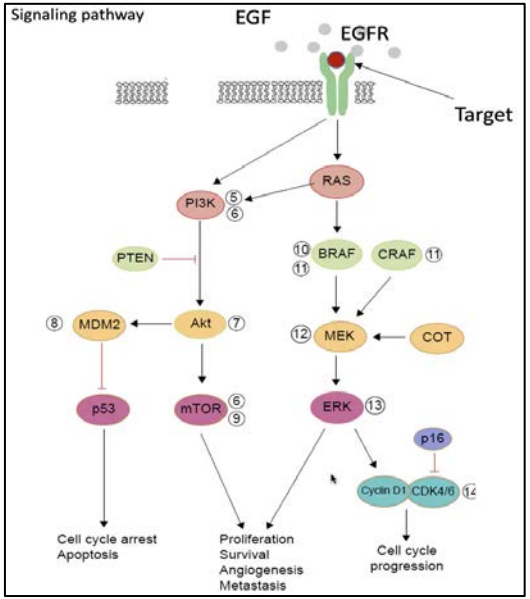
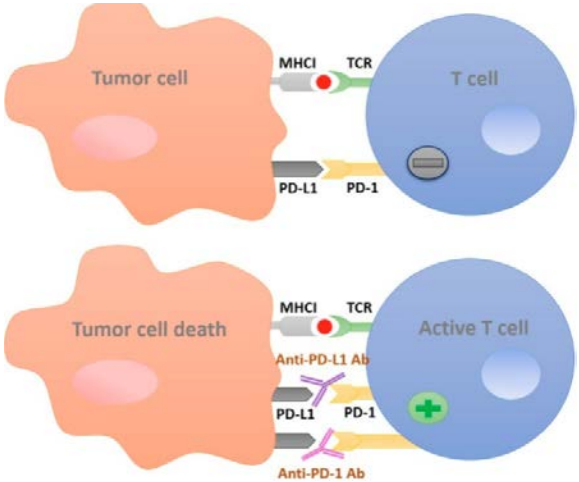


Источник: лекция № 3, курс “Онкоиммунология”, физический факультет, кафедра биофизики



Источник: Abdin SM, Zaher DM, Arafa EA, Omar HA. Tackling Cancer Resistance by Immunotherapy: Updated Clinical Impact and Safety of PD-1/PD-L1 Inhibitors. Cancers (Basel). 2018 Jan 25

Используется более 10 конечных точек

1) Overall survival	Общая выживаемость
2) Progression-free survival	Выживаемость без прогрессии
3) Disease-free survival	Выживаемость без заболевания
4) Event-free survival	Выживаемость без событий
5) Time to progression	Время до прогрессии

…

Overall Survival and Progression-Free Survival

Endpoint	Advantages	Disadvantages
Overall Survival	• Easily and precisely measured • Generally based on objective and quantitative assessment	• May be affected by switch-over of control to treatment or subsequent therapies • Needs longer follow-up • Includes noncancer deaths
Progression-Free Survival or Time to Progression	• Generally assessed earlier and with smaller sample size compared with survival studies • Measurement of stable disease included • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Balanced timing of assessments among treatment arms is critical • May not always correlate with survival

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FGA guide

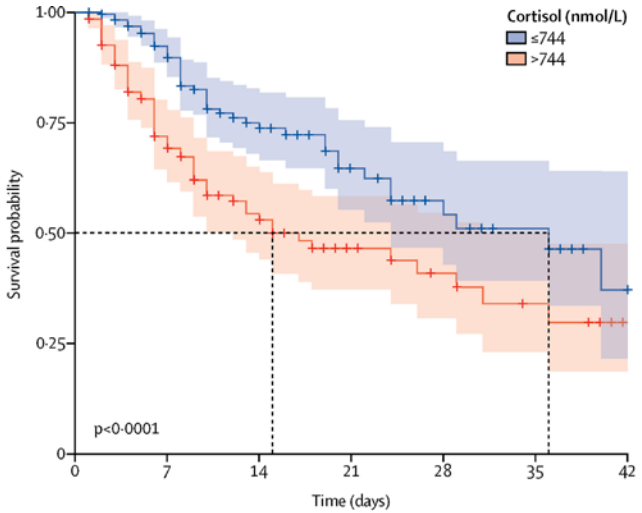
Данные по выживаемости

Subject_ID	PFS	Status_PFS	OS	Status_OS
1	336	0	365	0
2	127	0	225	1
3	333	1	355	0
4	52	1	241	1

Представленние данных по выживаемости

$$S(t) = \Pr(T > t)$$

$$\widehat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$



Number at risk (number of events)							
Cortisol >744	135 (0)	80 (39)	39 (53)	20 (57)	13 (59)	8 (61)	1 (62)
Cortisol ≤744	268 (0)	143 (19)	60 (38)	29 (43)	18 (47)	13 (48)	4 (50)

1.Association between high serum total cortisol concentrations and mortality from COVID-19; Tan, Tricia et al. The Lancet Diabetes & Endocrinology, Volume 8, Issue 8, 659 - 660

di - количество событий в момент времени ti
ni – число субъектов, подвергающихся риску непосредственно перед i-м временем (все, кто умер или “прошел цензуру” в это время или после него)

Оценка Каплана-Мейера (KM) - это типичная оценка, основанная на данных, предоставляющая кусочно-постоянную функцию S(t) и ее меру неопределенности

Цензурирование

Событие произошло

Цензурирование

Цель исследования

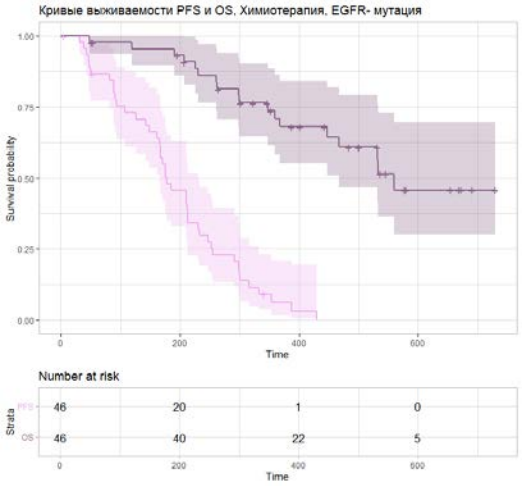
Цель: Исследование количественной взаимосвязи между суррогатными и клиническими конечными точками в онкологии

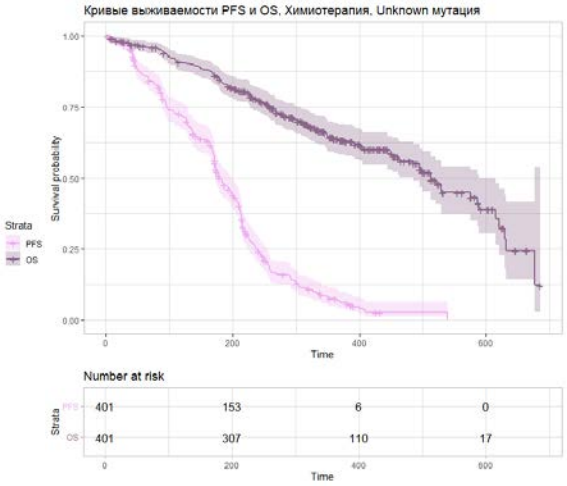
Корреляционный анализ выживаемости без прогрессии и общей выживаемости:

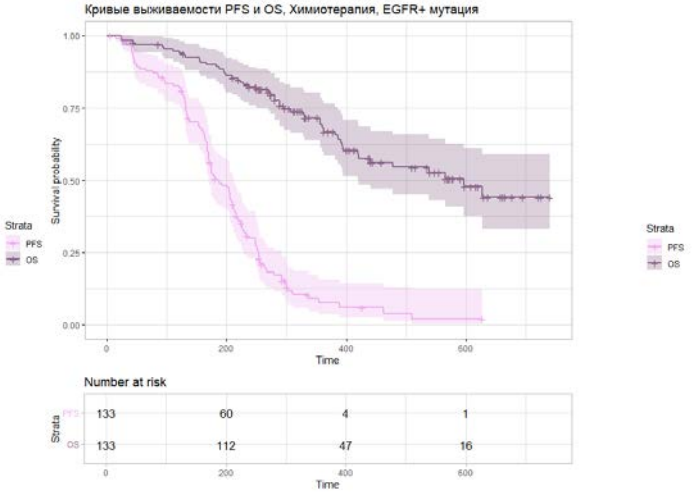
- выбор наборов данных для анализа
- изучение и применение методов корреляционного анализа
- интерпретация результатов

Кривые выживаемости Каплана-Мейера

Химиотерапия

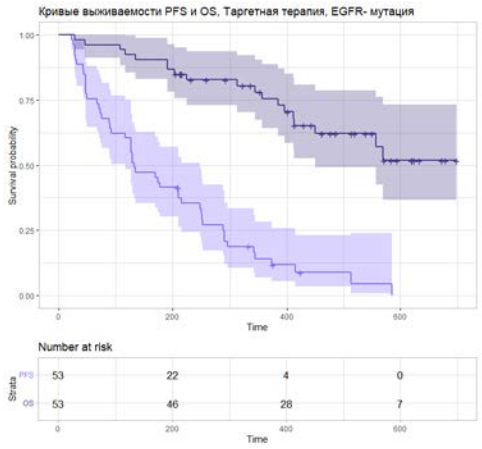


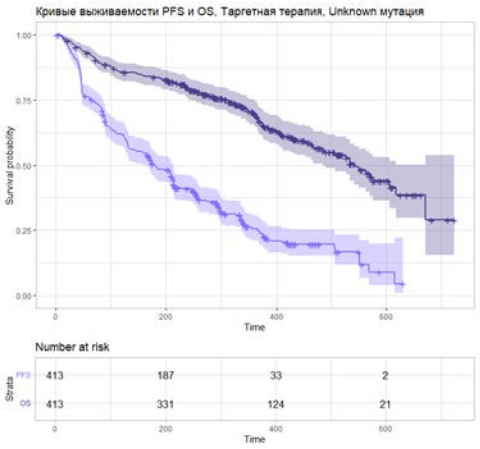


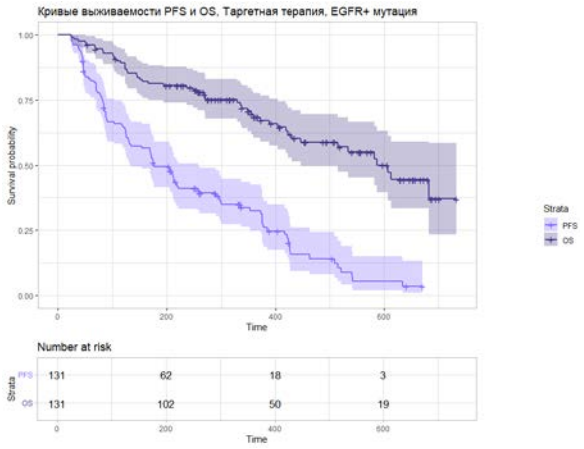


Кривые выживаемости Каплана-Мейера

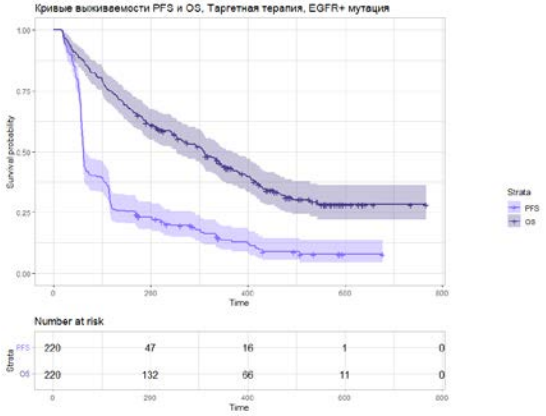
Таргетная терапия, испытание 1







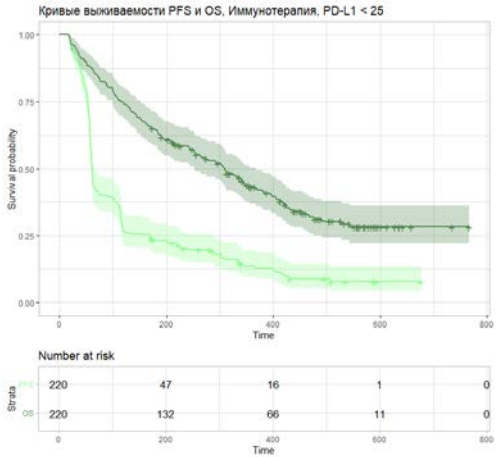
Таргетная терапия, испытание 2



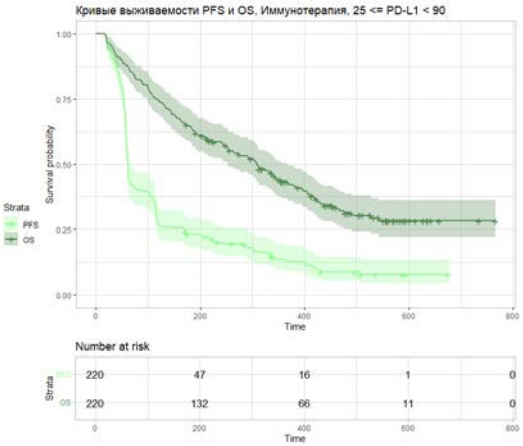
Каплан-Мейер

Кривые выживаемости PFS и OS

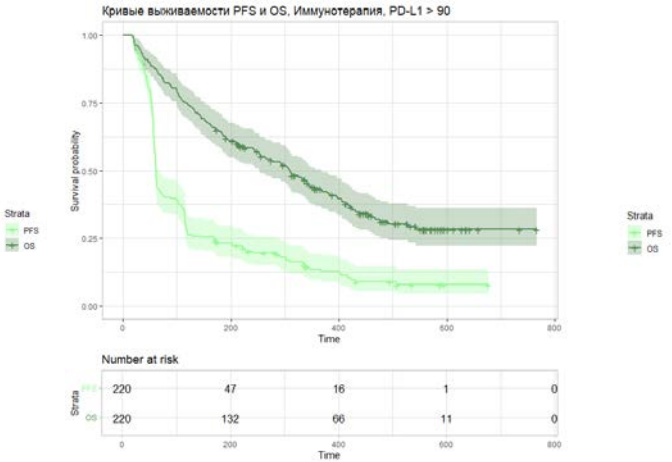
PD-L1 < 25



25 ⩽ PD-L1 < 90



PD-L1 ⩾ 90



Уровень экспрессии PD-L1 измеряется по шкале TPS (Tumor Proportion Score)

SurvCorr пакет в R

Usage

```
survcorr(formula1, formula2,
    data, methods = "imi", alpha = 0.05, intra = FALSE,
    M = 10, MCMCSteps = 10, epsilon = 0.001, maxiter = 100)
```

Arguments

`formula1`	Survival object for first time-to-event variable, e.g. `Surv(time1, status1)~1`
`formula2`	Survival object for second time-to-event variable, e.g. `Surv(time2, status2)~1`
`data`	Data set to look up variables
`methods`	Correlation method(s). Currently, only `"imi"` (iterative multiple imputation) is implemented.
`alpha`	One minus confidence level (for confidence interval computation)
`intra`	If TRUE, an intraclass correlation coefficient will be computed, assuming that the two time-to-event variables are interchangeable in each observation.
`M`	Number of imputations (for IMI)
`MCMCSteps`	Number of MCMCSteps (for IMI)
`epsilon`	Accuracy of numerical estimation of correlation coefficients
`maxiter`	Maximum number of iterations in IMI

Математическая реализация

- Для вычислений корреляций Пирсона используется алгоритм множественной импутации
- Вероятность выживаемости и времена цензурирования трансформируются с целью нормализации
- Величинам цензурирования присваиваются новые значения с использованием множественной импутации вплоть до достижения сходимости с заданной точностью

Результаты: Study 1 and Study 2

Type of therapy	**Rho** for **EGFR-** and CI (95%)	**Rho** for **Unknown** and CI (95%)	**Rho** for EGFR+ and CI (95%)
Химиотерапия (N=580), Study 1	0.52 (0.21; 0.73)	0.68 (0.59; 0.75)	0.67 (0.48; 0.79)
Таргетная терапия (N=597), Study 1	0.57 (0.22; 0.80)	0.78 (0.72; 0.84)	0.77 (0.62; 0.86)
Таргетная терапия (N=103), Study 2	-	-	0.86 (0.64; 0.95)

Study 1: NSCLC stage IIIb/IV, ECOG 0-1, line 1, asians
Study 2: NSCLC stage IIIb/IV, ECOG 0-1, line 1, white

Результаты: Study 3 (N=353), Иммунотерапия

Group	**Rho** and CI (95%)
PD-L1< 25	0.73 (0.65; 0.79)
25 ⩽ PD-L1 < 90	0.88 (0.81; 0.93)
PD-L1 ⩾ 90	0.70 (0.52; 0.83)

Study 3: NSCLC stage IIIb/IV, ECOG 0-1, line 2, white

Обсуждение применения данного подхода в литературе

Table 3 Individual-level association between real-world progression-free survival and overall survival in metastatic breast cancer (mBC) patients after diagnosis of mBC, according to mBC subtype

	Patients	ρ coef	95% CI
TN			
Chemotherapy only	1804	0.81	0.79 – 0.82
Chemotherapy and targeted therapy	921	0.73	0.69 – 0.76
HR + /HER2 +			
Chemotherapy only	84	0.33	0.12 – 0.52
Endocrine therapy only	342	0.43	0.32 – 0.53
Chemotherapy and endocrine therapy	85	0.72	0.58 – 0.82
Chemotherapy and targeted therapy	674	0.67	0.61 – 0.72
Chemotherapy, targeted therapy, and endocrine therapy	1036	0.78	0.74 – 0.82
Endocrine therapy and targeted therapy	228	0.71	0.61 – 0.78
HR – /HER2 +			
Chemotherapy only	75	0.67	0.51 – 0.78
Chemotherapy and targeted therapy	1164	0.81	0.78 – 0.84
HR + /HER2 –			
Chemotherapy only	1631	0.58	0.54 – 0.61
Endocrine therapy only	5545	0.66	0.64 – 0.68
Chemotherapy and endocrine therapy	3383	0.78	0.76 – 0.79
Chemotherapy and targeted therapy	699	0.45	0.39 – 0.51
Chemotherapy, targeted therapy and endocrine therapy	1518	0.70	0.67 – 0.73
Endocrine therapy and targeted therapy	492	0.61	0.51 – 0.70

Abbreviations: *mBC*, metastatic breast cancer; *HR +* , presence of hormone receptor; *HR –* , absence of hormone receptor; *HER2 +* , human epidermal growth factor receptor 2 (HER2) protein overexpression; HER2 – , no HER2 protein overexpression; *TN*, triple negative

Correlations are expressed as Spearman's *ρ* coefficient with 95% confidence interval (95% CI)

RESEARCH ARTICLE Open Access

Association between progression-free survival and overall survival in women receiving first-line treatment for metastatic breast cancer: evidence from the ESME real-world database

Coralie Courtinard[1,2], Sophie Gourgou[3,4], William Jacot[4,5,6], Matthieu Carton[7], Olivier Guérin[8], Laure Vacher[9], Aurélie Bertaut[10], Marie-Cécile Le Deley[11], David Pérol[12], Patricia Marino[13,14], Christelle Levy[15], Lionel Uwer[16], Geneviève Perrocheau[17], Renaud Schiappa[18], Florence Bachelot[19], Damien Parent[20], Mathias Breton[21], Thierry Petit[22], Thomas Filleron[23], Agnès Loeb[24], Simone Mathoulin Pélissier[1,25], Mathieu Robain[2], Suzette Delaloge[26] and Carine Bellera[1,25*]

cancers MDPI

Article

Real-World Therapy with Pembrolizumab: Outcomes and Surrogate Endpoints for Predicting Survival in Advanced Melanoma Patients in Germany

Peter Mohr [1], Emilie Scherrer [2], Chalid Assaf [3,4], Marc Bender [1], Carola Berking [5], Sheenu Chandwani [2], Thomas Eigentler [3,6], Imke Grimmelmann [7], Ralf Gutzmer [8], Sebastian Haferkamp [9], Jessica C. Hassel [10], Axel Hauschild [11], Rudolf Herbst [12], Ruixuan Jiang [2], Katharina C. Kähler [11], Clemens Krepler [2], Alexander Kreuter [13], Ulrike Leiter [6], Carmen Loquai [14], Friedegund Meier [15,16], Claudia Pföhler [17], Anja Rudolph [18], Dirk Schadendorf [19,20], Maximo Schiavone [19], Gaston Schley [21], Patrick Terheyden [22], Selma Ugurel [19], Jens Ulrich [23], Jochen Utikal [24,25], Carsten Weishaupt [26], Julia Welzel [27] and Michael Weichenthal [11,*]

Clinical Research Article

Combination of Mitotane and Locoregional Treatments in Low-Volume Metastatic Adrenocortical Carcinoma

Alice Boilève,[1,*] Elise Mathy,[1,*] Charles Roux,[2] Matthieu Faron,[3] Julien Hadoux,[1] Lambros Tselikas,[2] Abir Al Ghuzlan,[4] Ségolène Hescot,[5] Sophie Leboulleux,[1] Thierry de Baere,[2] Livia Lamartina,[1] Frédéric Deschamps,[2] and Eric Baudin[1]

Обсуждение

- Мы обнаружили корреляцию между PFS и OS в изученных данных. Наиболее сильная корреляция наблюдалась при таргетной терапии. Для имуннотерапии она была умеренной.

- Эти корреляции варьировались между исследуемыми группами, разделенные на страты по мутации EGFR или по уровню экспрессии PD-L1.

- PFS является менее информативной суррогатной конечной точкой для OS при химиотерапии

Актуальность научного вопроса

PFS – валидированная конечная точка для OS?

Frequently asked questions on surrogate endpoints in oncology-opportunities, pitfalls, and the way forward

Abhenil Mittal,[a] Myung Sun Kim,[b] Shenna Dunn,[c] Kristin Wright,[d] and Bishal Gyawali[d,e,f,]*

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[b]Hematology/Medical Oncology, Compass Oncology, Portland, OR, USA
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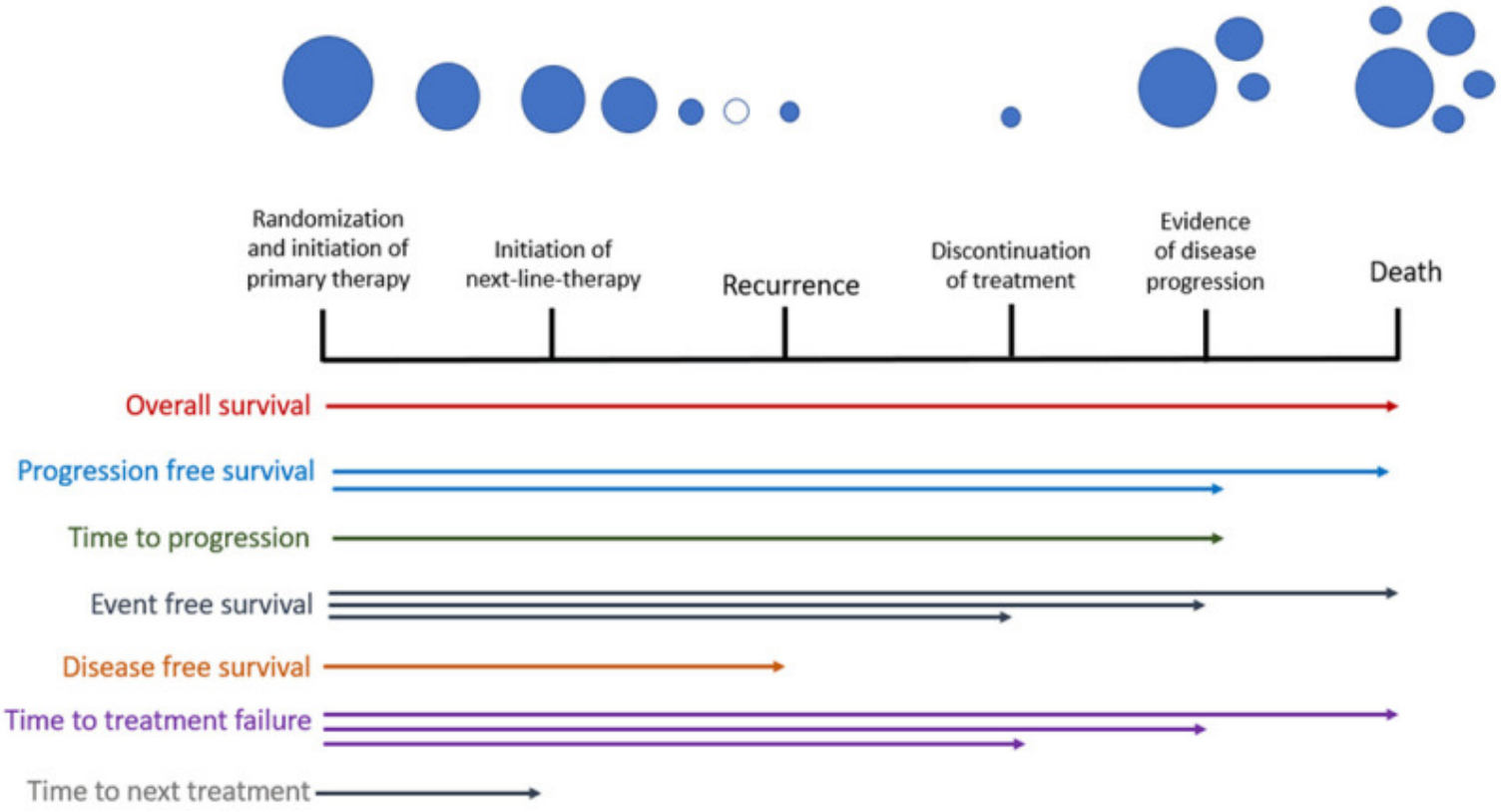
[f]Division of Cancer Care and Epidemiology, Queen's University, Kingston, Canada

Frequently asked questions on surrogate endpoints in oncology-opportunities, pitfalls, and the way forward Mittal, Abhenil et al. eClinicalMedicine, Volume 76, 102824

Спасибо за внимание!

Суррогатные и клинические конечные точки



Delgado A, Guddati AK. Clinical endpoints in oncology - a primer. Am J Cancer Res. 2021

Корреляция Пирсона

$$r_{xy} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

where

- n is sample size
- x_i, y_i are the individual sample points indexed with *i*
- $\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$ (the sample mean); and analogously for $\bar{y}$.

1. Нормальные распределения
2. Коэффициенты имеют значения от -1 до 1

Математическая реализация

- Пусть t_{1i}, t_{2i} - время событий и $\delta_{i1} = 1$ в случае если t_{1i} - цензурировано и $\delta_{i1} = 0$ в случае, если t_{1i} - не цензурировано. Пусть также S_k (t_k) - вероятность выживания

- Преобразуем t_{1i}, t_{2i} в нормально распределенные величины z_1 и z_2 для дальнейшего использования коэффициента Пирсона

$$z_1 = \Phi^{-1}\left(1 - \hat{S}_1(t_1)\right) \quad z_2 = \Phi^{-1}\left(1 - \hat{S}_2(t_2)\right)$$

Ф - функция нормального распределения
S - функция выживаемости

  - Пусть z_{1i} и z_{2i} - обозначают пары возможных цензурированных нормальных отклонений при статусах δ_{1i} δ_{2i}

  - Получение начального значения r_o корреляции Пирсона из нецензурированных пар z_{1i} и z_{2i}

Математическая реализация

Необходимо подготовить M датасетов с “нецензурированными” $z`_{1ij}$ и $z`_{2ij}$

- обе величины нецензурированы, оставляем так
- Одна из величин z1 или z2 - зацензурирована. Тогда “расцензурируем” нужную по следующему алгоритму:

$$z'_{1ij} \xleftarrow[z'_{1ij} > z_{1i}]{\text{RN}} N\left(r_0 z_{2i}, \left(1 - r_0^2\right)\right)$$

получает значение случайного числа из заданного распределения N, одномерного нормального распределения

- если обе величины “зацензурированны”, то выполнить поочередно по отноешнию к $z`_{1ij}$ и $z`_{2ij}$ предыдущий шаг

Математическая реализация

- Для каждого полученного M датасета с “нецензурированными” $z`_{1ij}$ и $z`_{2ij}$ получить r_j
- Повторить прошлые шаги, но с использованием r_j вместо r_o
- Итерационный процесс повторяется до сходимости rj в каждом наборе данных (в пределах желаемой точности ε)
- На последнем шаге мы преобразуем каждый rj по следующей формуле:

$$r_j^{(t)} = \tanh^{-1}(r_j). \text{ Далее } \bar{r}^{(t)} = M^{-1} \sum_j r_j^{(t)}$$

- Тогда финальным коэффициентом корреляции будет значение:

$$\hat{r}_w = \tanh\left(\bar{r}^{(t)}\right)$$

Additional slides:

Results: Study 3, Immunotherapy

Group	**Rho** for EGFR=0 and CI (95%)	**Rho** for EGFR=1 and CI (95%)	No separation and CI (95%)
1	0.749 (0.65; 0.82)	0.623 (0.35; 0.8)	0.729 (0.65; 0.79)
2	0.882 (0.79; 0.93)	0.74 (0.3 0.92)	0.882 (0.81; 0.93)
3	0.764 (0.55 0.88)	0.878 (0.39; 0.98)	0.705 (0.52; 0.83)

Additional slides:

(1) Let (z_{1i}, z_{2i}), $1 \leqslant i \leqslant n$, denote the pairs of possibly censored normal deviates of the original survival times of the sample, and the corresponding status indicators $(\delta_{1i}, \delta_{2i})$ as defined previously. Obtain a starting value r_0 of the Pearson correlation from uncensored pairs (z_{1i}, z_{2i}).

(2) Produce M data sets with 'uncensored' normal deviates z'_{1ij} and z'_{2ij} $(1 \leqslant i \leqslant n; 1 \leqslant j \leqslant M)$ as follows (for choice of M see end of Section 4):

- If both z_{1i} and z_{2i} are uncensored then $z'_{1ij} \leftarrow z_{1i}$ and $z'_{2ij} \leftarrow z_{2i}$, where $a \leftarrow b$ means a receiving the value of b.
- Censored z_{1i} and/or z_{2i} are made 'uncensored' by imputation, conditional on the censoring values z_{1i} and/or z_{2i}, and by using conditional normal distributions:

  (a) If only z_{1i} is censored then $z'_{1ij} \xleftarrow[z'_{1ij} > z_{1i}]{\text{RN}} N\left(r_0 z_{2i}, \left(1 - r_0^2\right)\right)$ and $z'_{2ij} \leftarrow z_{2i}$, where $a \xleftarrow[a>b]{\text{RN}} D$ means that a receives the value of a random number from the specified distribution D subject to the condition $a > b$. $N\left(r_0 z_{2i}, \left(1 - r_0^2\right)\right)$ is the univariate normal distribution resulting from slicing through the standard bivariate normal distribution parallel to the z_1-axis at the value of z_{2i}.

  (b) If only z_{2i} is censored then $z'_{1ij} \leftarrow z_{1i}$ and $z'_{2ij} \xleftarrow[z'_{2ij} > z_{2i}]{\text{RN}} N\left(r_0 z_{1i}, (1 - r_0^2)\right)$. Here, the univariate normal distribution results from slicing through the standard bivariate normal distribution parallel to the z_2-axis at the value of z_{1i}.

  (c) If both z_{1i} and z_{2i} are censored then a few steps (say 10) of iterating between (a) and (b) are required (more precisely, start with step (a), then step (b) with z_{1i} replaced by z'_{1ij} from the previous step, then step (a) again with z_{2i} replaced by z'_{2ij} from the previous step, then step (b) again with z_{1i} replaced by z'_{1ij} from the previous step, etc.). These Markov Chain Monte Carlo (MCMC) steps [19] permit to arrive at pairs of 'uncensored' normal deviates, representative for the respective sector of the bivariate standard normal distribution with working correlation r_0.

Additional slides:

(3) For each of the M data sets, obtain Pearson correlations $r_j (1 \leqslant j \leqslant M)$ from all now 'uncensored' normal deviates.

(4) For each of the M data sets, update the imputed z'_{1ij} and/or z'_{2ij} analogously to step 2, now using r_j instead of r_0. However, no new random number generation is needed: in fact the normally distributed random numbers in step 2 are based on underlying uniformly $U(0,1)$ distributed random numbers, and the latter are reused to update the normal deviates based on the most recent values of r_j, z'_{1ij}, and z'_{2ij}.

(5) The iterative process of updating the imputed normal deviates based on the current value of r_j within each of the M data sets and then of updating r_j based on the most current values of the normal deviates is repeated until convergence of r_j within each data set (within a desired precision ε).

(6) Finally, point and interval estimates of r_W are obtained based on the data completed at the final iteration step following Rubin [20]. Because the distribution of r generally is skew, each of the final r_j is transformed to $r_j^{(t)} = \tanh^{-1}(r_j)$. Then $\bar{r}^{(t)} = M^{-1} \sum_j r_j^{(t)}$, $\mathrm{var}\left(r_j^{(t)}\right) = (n-3)^{-1}$, and the between-imputation variance $B = (M-1)^{-1} \sum_j \left(r_j^{(t)} - \bar{r}^{(t)}\right)^2$. The total variance of $\bar{r}^{(t)}$ then follows as $T = (n-3)^{-1} + B(M+1)/M$. Now $\hat{r}_W = \tanh\left(\bar{r}^{(t)}\right)$, and the corresponding limits of a two-sided $100(1-\alpha)\%$ confidence interval are $\left[\tanh\left(\bar{r}^{(t)} \pm t_{df,\ 1-\alpha/2}\sqrt{T}\right)\right]$, with degrees of freedom $df = (M-1)\left[1 + M/\left(B(M+1)(n-3)\right)\right]^2$, again following Rubin [20].

Additional slides:

FDA guide

Endpoint	Advantages	Disadvantages
Overall Survival	• Easily and precisely measured • Generally based on objective and quantitative assessment	• May be affected by switch-over of control to treatment or subsequent therapies • Needs longer follow-up • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	• Generally assessed earlier and with smaller sample size compared with survival studies	• Blinding is important for assessing the endpoint • Potentially subject to assessment bias, particularly in open-label studies • Lack of validated instruments in many disease areas • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical
Disease-Free Survival or Event-Free Survival	• Generally assessed earlier and with smaller sample size compared with survival studies • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical • Includes noncancer deaths
Objective Response Rate	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Complete Response	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival