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Research Article

Historical comparison of survivals ? Why not ... (but only under certain conditions)

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Abstract

Background: Meanings, properties and possible implications of specific survival (SS) are worth exploring when computed from mortality tables, particularly by virtue of the relationship with excess mortality (ExcM) and expected mortality (ExpM).

Design: The variability of specific mortality (SM) and ExpM reflects the whole range of patients' fate, from the worst scenario (observed mortality higher than ExpM) to the best (SM equal to ExpM: a condition corresponding to full clinical recovery of the disease). Obviously, SM of patients and ExpM of reference population are conditioned by the same social and clinical factors, which act in parallel on both groups. So, the ExpM of reference subjects corresponds to the average age limit for a given historical period, to which the survival of patients can be normalized, also giving the possibility of post-hoc analysis of survival. SS, which results from the difference between observed and expected mortality, is also an index of the years of survival "stolen" by the disease with respect to the expected. All these times can be statistically compared by simple inferential tests.

Results: As an example of achievable result, we report a comparative analysis of two randomized trials, conducted in different times and closed several years ago, with identical target patients (advanced-stage Hodgkin lymphoma) and similar treatment (MEC ten-drug chemotherapy in the first study, and the similar CEC in the second, in which cyclophosphamide 650 mg/m2 replaced mechlorethamine 6 mg/m2). The analysis of SS revealed a previously underestimated statistical difference in favor of the patients treated with CEC: the difference seems tom be primarily due to the drug substitution, in spite of their presumed equivalence. Years of life lost per year of follow-up in CEC arm: 0.148 ± 0.228; in MEC arm: 0.411± 0.528 (P= 0.02314).

Conclusions: The comparative evaluation of SS offers more reliable results and is feasible in post-hoc investigations, even between different timeframes.

Keywords: Competing risks; Excess mortality; Historical comparison; Post-hoc analysis; Relative survival; Specific survival

Introduction

Overall survival (OS) is often the only time parameter which is analyzed in clinical studies, probably with the assumption that the large majority of deaths occurring in a cohort of patients are actually related to the disease under study. Thereby, an unquantifiable amount of approximation has to be accepted [1-2]. More properly, the impact of a severe illness on survival should be evaluated through the mortality due to, or associated with, the disease, i.e., by means of the specific survival (SS). However, the true causes of death are often difficult to establish with certainty, errors occur in nearly 20% of cases [3]. so, many authors accept all-cause mortality, especially if the number of deaths from other causes are presumably few. A further possibility is evaluating the

relative survival (RS), which estimates the observed mortality (OM) rate corrected by expected mortality (EpM) [2-5].

Our interest is mainly focused on the estimate of specific survival (SS), according to what proposed and debated by Nelson PC et al. [6] in relation to cardiovascular diseases and discussed by Cronin and Feuer [7] and by Lambert et al. [8] on the possibility of achieving more accurate estimates by means of the available population-based statistical methods. In particular, we followed what Pohar Perme et al. [9] suggested about the estimate of SS, performed by decomposing the OM into mortality due to the disease (excess mortality, ExcM, related to SS) and that due to other causes (ExpM, corresponding to the Expected Survival [ES] of the reference population). In terms of mortality the relation can be formulated as follows: OM = ExpM + ExcM. The possible presence also in the general reference population of deaths due to the same disease under study has been recognized, but has also been demonstrated to be negligible [1-9].

Interestingly, such relationship provides individual data of ExcM and, consequently, also of SS. This, furthermore, is obtained by simple calculation instead of the awearisome clinical evaluation of death certificates and of every other related medical document, a procedure judged as "flawed" [10], and "inaccurate" [11]. The advantage is that a specific information on individual causes of death- the main problem associated to the evaluation of cause-specific mortality- is not required. Exploiting the properties of the SS, and particularly of the ExpM, corresponding to the estimate of life expectancy, we found some conceptual insights and inferential possibilities that should make post-hoc comparisons of survival feasible, opening a slit on an analysis so far considered as a conceptual error.

Materials and Methods

Specific Survival and Excess Mortality

In cohorts of patients affected by cancer or by any other severe illness, a variable number of deaths occur unrelated to the disease under study: in order to get accurate clinical information, it would be more appropriate to assess and analyze only the proportion of mortality specifically due to the investigated disease, after the exclusion of deaths from any other causes: in other words, the SS should be considered [9-13]. The SS of each patient was obtained by the indirect technique that Pohar [9-12] and Seppä et al. [13-14] suggested with the aim of avoiding inaccuracy and misinterpretation linked to the evaluation of the clinical documents related to death. We used the existing relationships among observed mortality (OM), expected mortality (ExpM) and excess (or specific) mortality (ExcM) [1-8], determining the respective types of survival: OM = ExpM + ExcM and: ExcM = OM – ExpM (or: SS = OS – ExpS).

In this way the mortality related to SS (ExcM) can be obtained by subtracting the ExpM from the OM and such excess deaths can be attributed to the disease under study independently of the availability or reliability of clinical information on deaths [9]. Conceptually, the expected survival (ExpS) can be considered as the survival that would be expected by the patients in the absence of their particular disease- according to that experienced by the reference population and the difference (ExpS- SS) corresponds to the time stolen from patients by the disease. A severe disease can lead to a number of excess deaths much higher than that of ExpM, especially if the patients are young, i.e., with a long ExpS. Conversely, patients with a curable disease might have a SS or ExpS very close or even equal to the ExpS. Thus, the relationships between ExpM and ExcM can reflect the whole range of the prognostic variability of a disease, according to its distribution between both extremes.

Meanings And Properties Of Specific Survival

ExpS- i.e., the survival of the reference population corresponding for age, sex and calendar period of observation - can be considered both as the mean life duration of the normal subjects quite similar to the patient except for the disease, and as the average maximal time limit of survival attainable by all similar patients. Such a survival should also correspond to the mean whole time that patients might survive in the case of clinical recovery or effective treatment. Clearly, this kind of ceiling time, as the expected survival can be considered, may differ for the same disease according to the periods or countries under study. Nevertheless, we can assume as a postulate that, whatever historical time-frame and geographical area are considered, a cohort of patients of any illness cannot reasonably expect a mean survival longer than the ceiling time of their reference population. Exceptions to these assumptions are very improbable, since there are no clinical reasons why patients who have even perfectly recovered from their of diseases could expect to survive longer than healthy people (apart from hypothetical cases of a selective advantage acquisition by virtue of the disease itself). Thus, the deviation of the patient's observed survival from the expected survival (the ceiling time) can be interpreted as an absolute, standardized value and the efficacy of treatments might be evaluated by the degree of approach of the survival of patients to that of the comparable healthy subjects of the period. These concepts are the main basis of the comparability of patient series from different times and/or sites.

Expected and specific survival are subject to the same conditioning factors and evolve in parallel along time

Both patients -with their excess number of deaths (ExcM)- and the corresponding reference population, which provide the ExpM data, are naturally and equally contextualized in the whole

complex of the improving health care conditions as they are promoted by medical progress, public health service organization, social care programs, interacting with the customs, traditions and behaviors of the whole society. Such a contextualization allows the survival of the patients can be naturally normalized to the expected prognosis (ExpS) given by the corresponding reference population.

Specific and expected survival can have a clinical significance independent of the historical period of observation

In the light of the foregoing concepts, some assumptions can be made and summarized as follows.

- The SS and related mortality (ExcM) have ceiling values that are absolute mean limits of normal life expectancy for a given period. Obviously, we have to expect that they differ according to the period considered.
- The ExpS and related mortality (ExpM) of the reference populations are subject to the same environmental, nutritional, clinical and social factors as those affecting the SS of the corresponding cohorts of patients.
- If the variability of SS is naturally comprehended between full recovery and death, then the distance of any death from the corresponding life expectancy (ExpS) provides standardized measure of how much, in a given time or site, the maximally attainable ExpS of their time a has been approached.
- The number of years lost by patients with respect to normal life expectancy can be an indirect measure of the efficacy of treatments.

What can considerably affect the number of expected deaths in different historical periods is the degree of development of the whole civil progress; in the term "civil progress" any type of resources, facilities, skills, organization, know-how of every field of human knowledge are included, especially in the field of medicine. In view of these assumptions, we can handle the number of deaths of SS – related to those of ExpS – as absolute values. In other words, and limited to SS, the numbers of excess mortality from different groups of patients, and also from different times, can be reasonably compared, on condition that national or regional mortality tables for general population are available for each period of study, in order to allow the calculation of the expected survival for any considered period.

In a post-hoc comparison of SS the length of follow-up must be normalized, if not identical

Presently, the correspondence between patients of a study and reference subjects from the general population is required for sex, age, calendar time of observation, and race, whereever applicable. But for the purposes of a hypothetical post-hoc comparison of two cohorts of patients – allowed by the standard value assumed by ExpS- the number of deaths of a series has to be normalized to the different length of follow-up.Table 1 reports imaginary data to simply exemplify how a pair of subjects of the same sex, mean age and mean length of follow-up can show very different life expectancies according to whether a longer exposure to risk had been sustained by the younger or the elder patient. Thus, a post-hoc comparison requires that the number of the observed deaths in a series is first normalized by a factor accounting for the difference in the mean duration of the follow-up. We simply used the ratio between the mean follow-up times of the series under comparison, given the retrospective type of the research.

	Sex	Age at diagnosis	Years of f-up	Expected risk
(a)	M	30	10	0.015
Mean	M	50	20	0.241
	-------	-------	------	--------
	M	**40**	**15**	**0.256**
(b)	M	30	20	0,039
Mean	M	50	10	0.082
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	M	**40**	**15**	**0.121**

Table 1: Demonstration of how sometimes gender identity, besides equality of mean age and mean duration of f-up (follow-up) may not suffice to ensure equal exposure to risk (in "a" actually double that in "b").

In consideration (a) of the absolute ceiling value of the population-based ExpS, (b) that such a value shows a complete variability range from death to full recovery and (c) that in the same time period ExpS and SS are subject to the same external conditioning factors, then the difference between patients' SS

curves and the corresponding population's ExpS data can be handled as absolute values. The logrank test [15-17] seems to be acceptable as an inferential technique for this kind of comparison, because of its simplicity and good approximation (it is not an exact test, since the numbers of the expected deaths under comparison result from calculation instead of direct observation). When the time distance from ES is measured by the number of years lost per patient and per year of follow-up a Student's t test is sufficient. We performed the statistical analyses using the Stat View package (Abacus Concepts, 1918 Bonita Avenue, Berkeley, CA, 94704 – 1014, USA) for Apple Macintosh Computer (Apple Computer Inc., 20525 Mariani Avenue, Cupertino CA 95014 – 6299, USA). Some programs were partially modified and adapted to the requirements of the study.

Results From A Historical Comparison

Here we report an example of a direct comparison of two series of patients observed and treated in different periods, whose early and late results have already been assessed and published separately [18-22]. The identical clinical target- the treatment of advanced Hodgkin's lymphoma, stage II-B, III and IV, of whatever histological subtype, in patients aged 16-65 years- was investigated in the last two decades in two distinct Italian randomized clinical trials, performed in different timeframes, the second taking part of the results of the first into account. The databases of the two trials are now controlled and managed by the Federazione italiana linfomi (FIL), which has courtesy provided the data.

From 1996 to 2000 the Intergruppo italiano linfomi (IIL) conducted a three-arm clinical trial (355 patients enrolled) comparing three different multiple-agent chemotherapies: ABVD, Stanford-V and MOPPEBVCAD (MEC) [18-20]. The last schedule was found to be the most effective and the Guppo Italiano Studio Linfomi (GISL) decided to compare MEC, as the new promising protocol, with ABVD, as the well-known therapeutic gold standard for Hodgkin's lymphoma, and with BEACOPP, then considered a new emerging, very effective schedule. Three hundred and seven patients were treated in this second trial between 2000 to 2007 [21-22]. However, the cessation of the manifacturing of mechlorethamine, occurred just before the trial start, induced the investigators to replace the with cyclophosphamide [the acronym changed in COPPEBVCAD (CEC)]. The planned dose of cyclophosphamide was 650 mg/m^2, i.e. the dose that according to a consolidated practice - dating back to the seventies of the last century [23]- has constantly been considered to be endowed with an antitumor effect equivalent to that of the 6 mg/m^2 of mechlorethamine delivered with MEC. However, a direct clinical comparison of the efficacy of these two drugs has never been performed. Some of the main clinical characteristics of the two series are reported in (Table 2). while details regarding therapeutic schedules, response, early and late toxicity can be found in the original reports of each trial.

A preliminary direct, crude (and knowingly incorrect) comparison of the overall survival between the 107 patients treated with MEC and the 98 with CEC should not show a substantial difference (P > 0.250). Calculations for the comparison of SS of the two trials required four steps:

- The ExpM and ExpS of the patients of each series was assessed through the computation of the survival recorded in the Italian mortality registry (ISTAT) for subjects with the same sex, age, and along the same period of follow-up (see Appendix).
- For each patient of both trials the ExcM was obtained subtracting the ExpM from the OM.
- 3, The logrank test was applied to the distribution of the excess deaths obtained from step 1 and the distribution of excess deaths with a correction factor of 0.899 for the difference in the mean follow-up duration (see Appendix).
- The excess deaths determined from the calculations are the new uncensored observations to be graphed with all the remaining censored subjects of each group to obtain the SS curves (Figures 1 and 2).

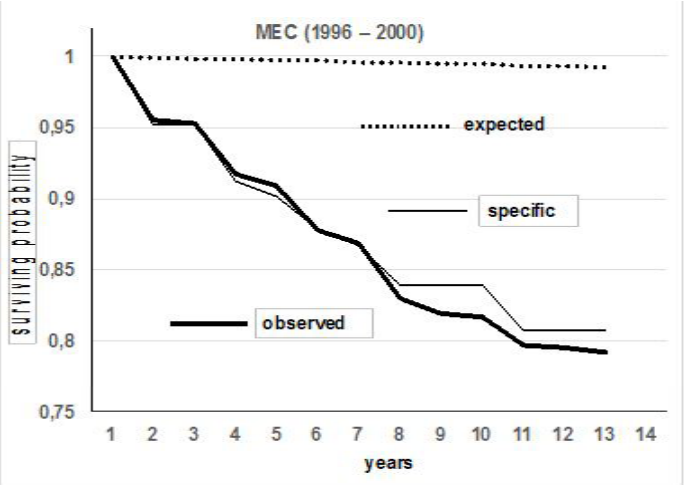

Figure 1: Observed, expected and specific survival of the MEC arm of randomization of the first trial (1996- 2000); for better clarity only the part of interest of the vertical axis has been graphed.

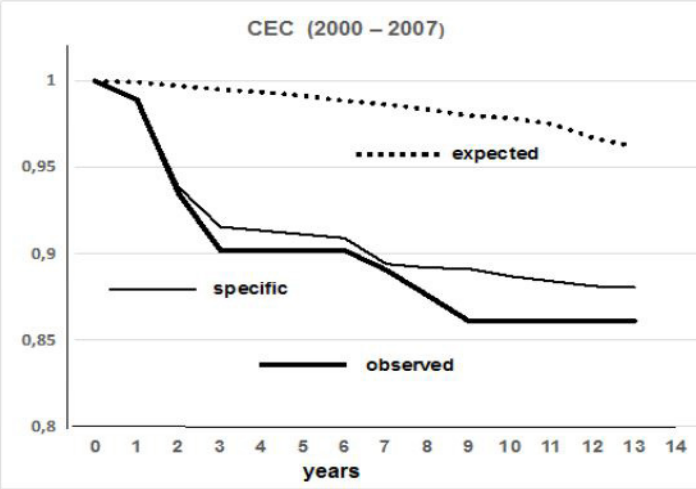

Figure 2: Observed, expected and specific survival of the CEC arm of randomization of the second trial (2000- 2007); for better clarity only the part of interest of the vertical axis has been graphed.

► For each patient the number (or fraction) of years lost during the whole time of follow-up was calculated subtracting the recorded actual survival from the life expectancy inferable from the mortality (Table 2).

	MEC	CEC
Timeframes of the studies	1996- 2000	2000- 2007
Patients treated	107	98
Males / Females	56 /51	56 /42
Age (median, range)	34.1 (16- 65)	34.7 (16- 65)
Follow-up of all patients	8.0 (1.0- 12.1)	8.9 (1.0- 13.8)
Follow-up of alive patients	8.3	9.7
Mean dose intensity administered	0.73	0.84
Complete remission	100 (94%)	85 (83%)
Observed deaths (any cause)	17	14

Table 2: Clinical characteristics of the two patient series involved in the comparison of survival.

The evaluation of SS revealed a slight but distinct- and unsuspected- difference in favor of the schedule containing Cyclophosphamide (CEC) with a $P < 0.02831$ (Figure 3).

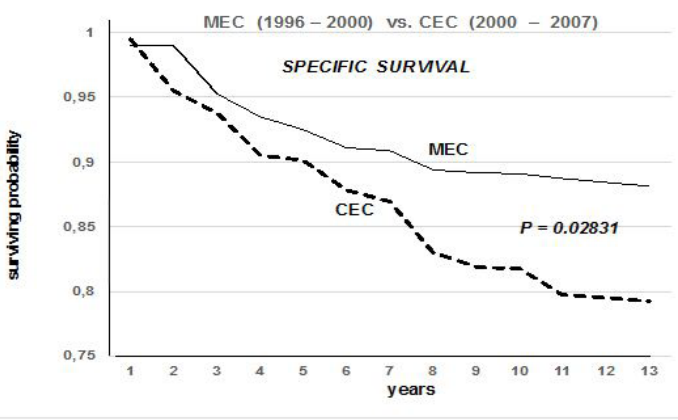

Figure 3: Comparison of the specific survivals of patients treated in independent arms of randomization of two distinct trials (MEC and CEC) of two distinct trials (MEC: 1996-2000 and CEC: 2000-2007); only the part of interest of the vertical axis has been graphed.

Compared with the mean life expectancy of each of the two groups the cumulative number of years lost was 67.87 for the patients in the MEC arm and 32,50 for those in the CEC arm. The difference of the number of years lost per patient and per year of follow-up (CEC: 0.148 ± 0.228; MEC: 0.411± 0.528) exceeds the first level of statistical significance (P=0.02314). It is, therefore, possible to think that CEC chemotherapy moved patients' survival closer to that expected than did MEC, possibly because of greater effectiveness and/or less toxicity of cyclophosphamide in comparison with mechlorethamine. Any case, their final clinical anti-lymphoma efficacy is not equivalent, as conventionally considered.

Discussion And Conclusions

Decomposing the OM into mortality due to the disease (ExcM) and mortality due to other causes (ExpM) reveals interesting and partially unexplored significance. After all the considerations made we should have to measure how much the survival of a cohort of patients has approached that of their healthy contemporary reference subjects.

Specific survival

What makes comparisons possible beyond temporal and

geographical differences are

- The ability of ExpS to reflect all the possible existential events within its variability range, its extreme values corresponding to recovery and death.

- The normalizing value that ExpS can assume. For the purpose of conmparison the inferential test should answer the question if the null hypothesis between the groups under analysis (i.e., no difference existing between them) has to be accepted or rejected, as far as the survival deviations of patients from the respective reference population are concerned.

Exposure to risk

An advantage of evaluating population-based SS is the easy handling of numbers of expected and observed events, and simple inferential tests. Although most randomized clinical trials do stratify patients for sex and age- factors also shared by the mortality tables from which SS ultimately derives - computation of the time of exposure to risk shows an additional great power of control on comparability, much more than afforded by conventional data usually given for the length of observation (mean or median follow-up, with or without standard deviations or range limits). Evaluation and control of individual exposure to risk is probably one of the most powerful tools for a good control of the comparability of the groups entering a clinical trial. In the present retrospective comparison of Hodgkin patients the death risk per patient was checked and found similar in both groups, and the difference in length of follow-up was adjusted with a proper correction factor.

Expected and specific survival rate

The reference population from which the ExpS is drawn can unavoidably include some subjects with the same disease being investigated: with high propbability some of the deaths given by the life-tables can be due to the same disease under study, making the reference population less than perfect. However, Ederer et al. [5] demonstrated that this can be considered a minor drawback, since it does not affect the correctness and precision of the estimates. Survival so calculated represents the ExpS of the comparable healthy subjects living in the same social framework, but it also corresponds to the mean survival that patients would have experienced if they had escaped the disease, or to which they could aim in the case of full recovery (survival advantages are not to be expected in patients with severe diseases, however perfectly cured). For this reason we assume that a hypothetical recovery cannot return to a patient more years of survival than those enjoyed by the comparable healthy subjects of his/her society.

Post-hoc comparisons

Variations of data recorded along time by mortality tables does not seem to be an obstacle to survival comparisons between different periods or sites. All those medical, social and individual factors generically contributing to wellbeing and health among people, are active in the cohort of patients under investigation as well as in the contemporary general healthy population. In other words, the progress (if any) acts equally on healthy and ill subjects of the civil society. Such an effect can vary over time, it can be positive or even negative, but its constant balance is a comparability guarantee, on condition that it is evaluated from the differences between the ExcM of the patients and the ExpM of the contemporary reference counterparts.

In conclusion, comparisons of OS among patients with the same disease, treated in clinical trials from different centres and/or different timeframes have generally been considered to be wrong procedures, so far, despite patients sharing the same characteristics. In fact, a number of collateral conditions and minor factors can differ in relation to the period of a study, such as supportive therapies, diagnostic accuracy, hygienic and nutritional aspects, efficiency of the general practitioner network, quality of home nursing services and probably many others. The complexity of these parameters precludes the possibility of an "a priori" computation when designing a therapeutic protocol and planning the related data recording system. However, the interest in a post-hoc comparison of survival between similar patients from different clinical studies may arise from the perception (or doubt) that a substantial advantage could exist and might be demonstrated among many minor aspects-not accounted by the original studies and until then unconsidered in the clinical practice- involving patient randomization, treatment, evaluation of response, criteria of conditional intervention, post-treatment follow-up and a number of clinical features unforeseen in the design of the trial. Here we suggest how this problem can be approached giving also a simple example.

Sometimes, a comparison of our current working standards with past clinical experience may offer interesting new views on the scientific roots of our present progress and useful clues for future clinical strategies [2-24]. Certain old drugs, some presently disregarded procedures, out of use diagnostic tools, different treatment combinations, all those clinical matters considered out-of-date by some investigators but supported and advocated by some others, those issues that should require randomized studies, but would lead to economically unfeasible or nearly utopian trials, all these are potentially objects of historical comparisons that the

technique described here makes possible with sufficient accuracy and caution.

Appendix

Assessing the Expected Mortality (EM)

For each patient and for each year of follow-up (or fraction of year) we must apply and sum all the appropriate yearly mortality rates (Ox) recorded from the mortality registries for people with the same sex and age, taking into account the increase of age at the birthdate: so, we have to apply a given rate for the first part of the year until the birthday and another rate for the remaining part.

Example: a male, born in August 1st, 1926, who survived the whole 1997 should have the mortality rate of a 70-year-old subject (0.03063) during the first 212 days of 1997, and then the rate of a 71-old subject (0.03376) in the remaining 153 days. Of course, fractional numbers of ExpM must be accepted. So, the ExpM related to the whole 1997 is the following:

0,03063 x 212/365 + 0,03376 x 153/365 = 0,03194 (Ox of 1997)

Data of specific survival and graphication

The ExcM (the mortality entering the Specific Survival [SS]) can be obtained by subtraction of Expected Mortality (ExpM) from the Observed mortality (OM) for all the patients in each year of follow-up. The excess deaths obtained by calculation have to be graphed as uncensored observations. The points of the curve so calculated are necessarily yearly, and the curve will be actuarial.

Normalization

The numbers of deaths of one cohort of patients must be corrected by the ratio between the mean length of the follow-up of the two series. In detail, we multiplied the numbers of yearly calculated deaths of SM in the CEC series by 7.980/8.877, so obtaining a correction factor of 0.899.

Inferential tests

The distribution of the excess deaths in the compared groups can be statistically evaluated by a chi-squared test, year per year, or cumulatively at the end of follow-up. It is based on the common evaluation of the number of observed and expected deaths in both groups.

$$\frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2}$$

In this case, the "Observed" deaths (O) are those directly derived in each group from the subtraction OS- ES (and in one group after normalization of the number of observed deaths with application of the correction factor), while "Expected" deaths (E) are those specific deaths required by each group if their distribution would have been proportional to the number of patients at risk in each group.

It is advisable to arrest the progressive, every-year calculation of such a chi-squared test when the number of patients in both arms become less than 40. The time distances between observed and expected survival must be recorded as years lost per individual patient and per year of follow-up. In each year of follow-up it is accepted that those censored patients whose date of exit from the study is unknown can contribute to survival for half a year as a mean. These data regarding the distance from ExpS can be evaluated by a Student's t test.

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