A STUDY OF TUMOR DOUBLING TIME AND CANCER SURVIVAL

ABSTRACT

Background

Early detection and treatment are accepted as primary strategies for effective cancer therapies. I challenge the validity of these strategies.

Methods

A theoretical group of 974,447,314 subjects were evaluated with a mean tumor doubling time of 171.5 days and a standard deviation of 79.6 days. All subjects are assumed to have the same baseline characteristics, except for the tumor doubling time, and to have developed their cancers from a single progenitor cell (0.01 mm tumor). The tumor size is calculated every week for 80 years and survival rates are calculated under various conditions, which include the identifiable tumor size on examination, the size at which the tumor causes death, and the interval of examination.

Results and Conclusions

Cancers detected at a small size have better 5-year survival rates than those found at a larger size, even if no treatment is given. One reason for this observation is that cancers found at a small size have longer tumor doubling times. Another reason is that cancers found at a small size will take longer to reach a stage at which mortality would be predicted. However, the validity of early detection and early treatment as an effective clinical intervention for cancer therapy can't be verified by the fact that early-detected cancers have better 5-year survival rates alone. Large-scale randomized clinical studies between two groups, one that has early detection and early treatment and the other that has early detection and no treatment, are needed to verify the efficacy of this guiding principle.

METHODS

The practical treatment of patients with cancer reveals that some individuals die in a short period of time, but some survive for much longer periods. Notably, this phenomenon occurs even among patients with the same histological type and stage of cancer. It is known that some cancers grow rapidly whereas others grow much more slowly which can be readily assessed by the tumor doubling time.

The doubling times for a range of given tumor types have not so far been accurately determined, but there have been some reports of such measurements in the literature. For example, it has been shown that the mean tumor doubling time for invasive breast cancer is approximately 130 days [1]. Other studies have reported that the mean tumor doubling time for lung cancer in an assessment of 237 patients is 166.3 days [2]. Moreover, the mean tumor doubling time for primary melanoma was found to be 144 days (range, 50-377 days), and for metastatic melanoma to be 64 days (range, 8-212 days) [3].

Tumor doubling times thus range from 8 to 377 days [3] and a range of 365 days was therefore assumed in these analyses for simplicity and the fact that it is within the measured range. 166.3 days was adopted as the mean value based upon the findings reported in reference 2.

The NORMINV function of Microsoft Excel was used 364.0390639=NORMINV (0.99, 166.3, 85) and shows that 99% of the doubling times can be measured within 364.0390639 (almost one year), when the standard deviation is set at 85 days with a mean of 166.3 days. I assume a group of 1,000,000,000 subjects. A discrete normal distribution is used with tumor doubling times measured in days. Using the NORMDIST function of Microsoft Excel, the number of subjects for each tumor doubling time was calculated from:

B=INT(NORMDIST (A, 166.3, 85, FALSE) * 10 ^ 9)

where A is the tumor doubling time in days and B is the number of subjects. From this calculation, a single day was found to be the shortest tumor doubling time for 708,379 subjects, and 637 days to be the longest tumor doubling time for a single subject. It was also found that if the total number of subjects is adjusted to 974,447,314, the mean changes to 171.5 and the standard deviation becomes 79.6, as a discrete distribution and not a continuous distribution is then assumed. The number of subjects is truncated at the first digit after the decimal point.

This group of 974,447,314 subjects is assumed to be matched for race, sex, height, weight, health i.e. all characteristics except for the tumor doubling time.

All subjects are proposed to begin with a single cancer cell of about 0.01mm in diameter, such that all subjects are presumed to begin with a 0.01mm tumor.

The tumor size was calculated every week for 80 years according to the following formula:

dimBeginningSize=0.01
dimDays = (52 * (dimYears - 1) + dimWeeks) * 7
dimTumorSize = dimBeginningSize *(2^(dimDays / dimDoublingTime))^(1/3)

dimDays: days (unit: day)
dimYears: years (unit: year)
dimWeeks: weeks (unit: week)
dimTumorSize: tumor size (unit: mm)
dimBeginningSize: beginning size (unit: mm)
dimDoublingTime: tumor doubling time (unit: day).

The survival rate was then calculated under various conditions. Three variables were set for the conditions in which the survival rate was calculated. These variables include the identifiable tumor size on examination (unit: mm), the size at which the tumor causes death (unit: mm), and the interval of examination (unit: year). The values 5, 7, 10, 15, 20, and 30 was assigned for identifiable tumor size on examination; 100, 150, and 200 for the size at which the tumor causes death; and 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 for the examination intervals. In this study, examination is designated as CT, MRI, or PET.

In reality, cancer stages cannot be determined by tumor size alone. The intention in these analyses, however, was to calculate the extent of cancer growth using a computer algorithm. Hence, the stages are defined only by tumor size. This is a reasonable stage division in this case, because the subjects are assumed to have the same characteristics except for differences in their tumor doubling time. The size of the cancer has been set for each stage on the basis that the patients can be classified equally into four groups. The stages are thus defined as follows:

stage 1, <13mm
stage 2, 13mm and <20mm
stage 3, 20mm and <40mm
stage 4, 40mm and >40mm

When some subjects die without cancer detection, they are considered to have been identified on the week of their death.

The variables employed in these analyses are listed in the following order: the identifiable tumor size on examination, the size at which the tumor causes death, and the interval of examination. Thus, a label of “10_150_1” means that the identifiable tumor size upon examination is 10mm in diameter, the size at which the tumor causes death is 150mm, and the interval of examination is 1 year. C stands for change. A label of “10_150_C” indicates that the identifiable tumor size upon examination is 10mm in diameter, the size at which the tumor causes death is 150mm, and the interval of examination has changed.

RESULTS AND DISCUSSION

The 100_150_1 data in Table 2 indicate that stage 1 cancers have a 70.8% 5-year survival rate with a 11.4mm mean discovered tumor size, stage 2 have a 31.6% 5-year survival rate with a 15.2mm mean discovered tumor size, stage 3 have a 0% 5-year survival rate with a 26.2mm mean discovered tumor size, and that stage 4 lesions are associated with a 0% 5-year survival rate with a 99.3mm mean discovered tumor size. This suggests that a patient with cancer that is discovered early has a better 5-year survival rate and therefore better prognosis. This holds true even if the detectable cancer size is changed or the size at which the tumor causes death is changed. Table 2 also shows that 241,769,974 subjects are found at stage 4, when they are examined every 5 years and that 32,900,631 subjects have stage 4 lesions when they are examined every year. This indicates that 208,869,343 subjects (241,769,974-32,900,631=208,869,343) are newly found at earlier stages when they are examined every year. This gives the impression that frequent examination saves many lives. Therefore early detection and treatment is a desired strategy for cancer treatment. However, it must be noted that the number of weeks to death (whole weeks from the first single cancer cell to death) is the same whether they are discovered early or late when no treatment is given (Table 4).

Early stage tumors have longer doubling times when compared with later stage cancers. The 100_150_1 data in table 2 indicate that stage 1 cancers have a 207 day doubling time, stage 2 have a 152 day doubling time, stage 3 a 68 day doubling time, and that stage 4 lesions have a 26 day doubling time. It is very difficult to identify tumors with short doubling times at their early stages because they grow rapidly. Even when yearly examinations occur, rapidly growing cancers with short doubling times can become large during the intervening 12 month period. It can be said that small-sized tumors at early stages have long doubling times and that large-sized tumors at late stages have short doubling times. Small tumors discovered early have more time before they reach the size at which mortality is predicted and the contrary is true of large lesions. This is another reason that the 5-year survival rate is better for patients with cancers that have been discovered early.

Table 3 shows that longer intervals between examinations reduce the 5-year survival rates. For example, a 1-year interval between examinations is associated with a 35.4% 5-year survival rate but a 10-year interval has an 8.5% 5-year survival rate. This certainly suggests that more frequent examinations promote a better 5-year survival rate. However the weeks to death are equivalent regardless of whether given frequent examinations occur. Frequent examinations make it possible to discover small tumors and result in an improved 5-year survival rate with the same weeks to death.

Recently, PET has become a popular diagnostic tool and smaller cancers are being detected using this methodology. Improved 5-year survival rates can be obtained when cancers are detected at smaller sizes as shown in Table 5. For example, in C_100_1 subjects, the 5-year survival rate is 56.9% when the identifiable size is 5 mm, whereas it falls to 35.4% when the identifiable size is 10 mm. The weeks to death are the same whether smaller cancers are detected or not because no treatment is given. Hence, when small cancers are detected, the 5-year survival rates improve remarkably but the time to death can remain the same.

Cancers detected at a small size have a better 5-year survival rate than those detected at a larger size, even if patients are given no treatment. The fact that cancers detected at a small size have a better 5-year survival rate doesn't validate early detection and early treatment as a requirement for increased survival rates however, because early detection alone can bring about a better 5-year survival rate. A large-scale randomized clinical study is needed to verify the advantages of an early detection and early treatment policy. In this proposed study, one group would be given early treatment with early detection and another group is observed that had early detection but no intervention. It would, however, be difficult to find patients who had refused treatment and could be recruited into this second group of subjects and ethical problems may arise with the analysis of

such a grouping.

REFERENCES

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