Tumor control, probability of cure, and all that.

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Conventional view of TCP (Munro-Gilbert):

- TCP is identified with the cellular extinction probability, $P_0(T)$, at the end of a treatment of duration $T$;
- The number of clonogens surviving treatment is Binomial/Poisson distributed:

$$TCP(D) = \left[1 - S(D)\right]^n \approx \exp[-n \ S(D)] = \exp[-\bar{n}(D)]$$

$$\bar{n} \ (D) = \text{expected number of clonogens surviving a radiation dose} \ D$$
Assuming constant birth (b) and spontaneous death (d) rates:

\[ S(t) = S_0(t) e^{(b-d)t} = S_0(t) e^{\lambda t} \]

\( S_0(t) \) is the survival probability in the absence of cell proliferation and death (b=d=0).

Cell loss factor: \( \varphi = \frac{d}{b} \)

\[ b = \frac{\log(2)}{T_{pot}} \quad T_d = \frac{T_{pot}}{1 - \varphi} \]

b and d are independently obtainable.
It is immediately obvious that the Munro-Gilbert TCP expression cannot be right:

\[ TCP(D) = \left[ 1 - S_0(t)e^{\lambda t} \right]^n \]

>1 at large \( t \)

although one would (and usually does) fail to notice this if the Poisson approximation is used instead:

\[ TCP(D) = \exp \left[ -nS_0(t)e^{\lambda t} \right] \]
TCP thus defined has **significant** deficiencies:

- What matters is the presence (or absence) of a *detectable* or *symptomatic* tumor  
- $n(D)$ is an *unobservable* quantity,  
- Elimination of *all* malignant clonogenic cells is a sufficient but in most cases *unnecessary condition of cure* (e.g. small tumors may undergo spontaneous regression),  
- Many primary cancers, such as breast and prostate cancer, are not lethal *per se*. They kill through metastases; therefore, an object of tumor control in such cases should be the prevention of metastatic spread of the disease.
Here we are concerned with the *probability of cure* (long term recurrence-free survival) rather than extinction of clonogenic tumor cells at the end of treatment.
We wish to:

- Establish a link between survival time – where the events of interest are local recurrence or distant (metastatic) failure (cancer-free survival) or death (cancer-specific survival) – and the distribution, $P_m(t)$, of the number of clonogens that remain alive at a certain time $t$ after initiation of treatment,
- Link $P_m(t)$ to treatment planning and tumor-specific parameters
- Extrapolate TCP to other treatment modalities (e.g. changed dosage or temporal pattern of dose delivery, different radiation quality), replace BED with IED.
The distribution of tumor recurrence times, $P_m(t)$, is obtainable from empirical (clinical) data on:

- primary tumor recurrence
- metastatic relapse
- cancer-specific death
Assuming that for each surviving clonogen \textit{potential progression times} to tumor recurrence are \textit{independent} and \textit{identically} distributed random variables, and also independent of the number, \( M \), of surviving clonogens at the end of treatment, the recurrence-free survival at time \( t \) post treatment, \( G(t) = \Pr(\tau \geq t) \), where \( \tau \) is the time to recurrence, can be calculated as follows:

\[
G(t) = \sum_{m=0}^{\infty} P_m(T) \left[ G_1(t) \right]^m
\]

- \( G_1(t) \) is the probability that an individual clonogen did not grow into a detectable tumor by time \( t \).
- \( P_m(T) \) is the probability that \( m \) malignant clonogenic cells survive the treatment.
Note the following:

- The **entire distribution** of the number of surviving clonogens rather than the extinction probability $P_0(T) = Pr(M = 0)$ alone is needed.
- Assuming that the distribution of the clonogenic progression time is **proper** $G_1(\infty) = 0$, i.e. over a very long period of time every surviving clonogen gives rise to an overt tumor with probability 1.
- If dormancy times for some surviving clonogens are long $G_1(\infty) = 1 - p$, where $p = Pr\{\tau = \infty\} > 0$
- If $M$ is Poisson distributed: $G(\infty) = e^{-\bar{n}(D)p}$

Mean number of clonogens surviving treatment
The probability that a population of $m$ surviving clonogens with post-treatment birth and death rates $b$ and $d$ ever reaches size $N > m$ is given by

$$P_N(m) = \frac{(d/b)^m - 1}{(d/b)^N - 1}$$

$$G(\infty) = \sum_{m=0}^{N-1} P_m(T)[1 - P_N(m)] = \sum_{m=0}^{N-1} P_m(T)\frac{(d/b)^m - (d/b)^N}{1 - (d/b)^N}$$

$N$ is of the order of $10^4$-$10^9$

Cell loss factor: 0.9

$$G(\infty) \approx \sum_{m=0}^{\infty} P_m(T)\left(\frac{d}{b}\right)^m$$

extinction probability of a population of $m$ cells
In the absence of radiation exposure:

\[
P_0(t) = \left\lfloor 1 - \frac{1}{e^{-\lambda t} + \frac{b}{\lambda} \left[ 1 - e^{-\lambda t} \right]} \right\rfloor^n
\]

The long-term *spontaneous cure probability* of a tumor containing n cells is:

\[
P_0(\infty) = \left( \frac{d}{b} \right)^n
\]
If the treatment duration is $T$ then the cure probability is:

$$P_0(\infty) = \left[ 1 - \frac{1}{\int_0^T b \frac{du}{S_0(u) e^{\lambda u}} + b \frac{e^{-\lambda T}}{\lambda S_0(T)}} \right]^n$$

Otherwise (e.g. permanent implant):

$$P_0(\infty) = \left[ 1 - \frac{1}{\int_0^\infty b \frac{du}{S_0(u) e^{\lambda u}}} \right]^n$$
Example: for a treatment consisting of two fractions separated by the time interval $T$:

$$P_0(\infty) = \left[ 1 - \frac{S_0^2 e^{\lambda T}}{b \left\{ S_0 \left( e^{\lambda T} - 1 \right) + 1 \right\}} \right]^n$$

whilst according to the Munro-Gilbert expression:

$$P_0(t) = \left[ 1 - S_0^2 e^{\lambda t} \right]^n \quad t \geq T$$

Note that as $t \to \infty$ this expression becomes meaningless.
In terms of cure rate, two or more treatments are biologically equivalent if they have the same effective survival:

\[ S = \frac{1}{b \int_{0}^{\infty} \frac{du}{S_0(u)} e^{\lambda u}} \]

This is about all there is in radiobiology in this respect.
The concept of BED (which we do not advocate) compels the user to apply the LQ model and, in the process of doing so, collects all LQ problems:

\[ TCP = \left(1 - e^{-\alpha_{BED}}\right)^n \]

\[ IED(\infty) = \frac{1}{\alpha} \log \left[ b \int_{0}^{\infty} \frac{du}{S_0(u) e^{\lambda u}} \right] \]

or, according to M-G:

\[ BED(t) = -\frac{1}{\alpha} \log \left[ S_0(t) e^{\lambda t} \right] \]

Note that at large \( t \) BED becomes negative!! Also, IED depends on both \( \lambda \) and \( b \).
The real reason for using such quantities as IED or BED to construct equivalent treatments is that they circumvent the need to know the actual initial number of malignant cells, n. On the other hand, the applicability of BED as a substitute for IED does depend on n (among other factors) and this is the main reason BED should be avoided. The other reason is that the extension of BED to larger values of t eventually becomes meaningless.

Numerical example (permanent implant):

BED($t_{\text{eff}}$)=125 Gy
IED($\infty$)=138 Gy

\[
t_{\text{eff}} = -\frac{1}{\lambda} \log \left( \frac{b}{\alpha D \lambda} \right)
\]

(Dale, 1989)
Unresolved questions with respect to NTCP:

- *Mechanistic* NTCP models remain largely unavailable.
- It is reasonable to assume that the total number of cells inactivated determines the clinical outcome for tumors, but not for organs at risk, primarily because for these structures *function* is the key clinical outcome.
The take-home message:

• What matters when we speak of tumor control is the probability of overall long-term survival.

• For patients for whom cancer is essentially the main cause of death, cause-specific survival (net survival) is the quantity of interest.

• For patients who are at significant risk of dying from other causes, we shall need to consider the treatment effect on crude (rather than net) survival because this is a better measure of its overall result.

• One shall then work out a treatment which will reduce the probability of long-term local or distant failure – both defined by the presence of a detectable or symptomatic life-threatening malignancy.