Abstract. Purpose: Prostate-specific antigen (PSA) doubling-time (PSA-DT) is an important indicator of progression and survival in men with prostate cancer. Three major limitations regarding PSA-DT determination may lead to inconsistent results: the variety of mathematical methods currently applied, the non-standardized handling of input variables and the potential lack of accuracy due to PSA variability. The aim of this project was to develop a reproducible PSA-DT determination tool which simultaneously provides a PSA-DT error estimation. Materials and Methods: An internet-based PSA-DT calculation tool via nonlinear optimization implementing the least squares error method using the most recent three PSA values was developed. PSA-DT calculation error is estimated via randomly disturbed measurement data streams (n=65) based on a variable (5-25%) PSA variability. Results: According to a simulation in five men, PSA-DT was calculated to be between 1.7 and 15 month (mean: 6.3 month) and determined with another standard tool between 1.3 and 14.5 month (mean: 4.2 month). Conclusion: We present a defined, open and reproducible PSA-DT calculation and PSA-DT error estimation tool based on a standardized PSA data input. This tool is not better compared to other methods but is scientifically standardized and freely accessible via the following internet address: http://adam.drahtwarenhandlung.at/webapp/mg2008/chapter_prostata4/example_psa.

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Based on the observation that prostate-specific-antigen (PSA) follows an exponential growth curve in men with prostate cancer (PC), PSA doubling-time (PSA-DT) has been investigated as potential predictor of major clinical endpoints at different stages of PC (1, 2). As a powerful parameter to estimate the natural course of PC, it is currently used in active surveillance protocols and, for instance, in the assessment of patients with biochemical recurrence following local treatment (3-10).

In contrast to the broad evidence for the prognostic value of PSA-DT, the methodology of calculation is inconsistent (11, 12). Depending on the applied mathematical method, PSA-DT may vary significantly, thus potentially creating incomparable information regarding further treatment. In addition, PSA-DT accuracy is dependent on a variety of factors, mainly on PSA variation, the time interval between PSA measurements and the total number of PSA values used (13, 14).

The following project aimed to develop a reproducible method for PSA-DT determination, including standardized data input, and to provide a reliable PSA-DT error estimation. Based on PSA-DT error estimation, individual decisions on further PSA determination to increase accuracy can be made and the time required to obtain reliable results can be minimized.

A well-defined and comparable PSA-DT calculation methodology represents an important basic tool in scientific settings, as well as in everyday clinical routine use. It has to be emphasized that our tool is not aimed to be better compared to existing methods but provides a standardized, defined and reproducible method, also providing the PSA-DT error range resulting from PSA variation.
Materials and Methods

PSA-DT calculation. Based on the most recent three PSA measurements (for the following formula characterized as: a, b, c), a nonlinear optimization based on the least squares error method was implemented for calculation:

\[ f(\text{time}) = a + b \times \exp(c \times \text{time}) \]

The target value of the PSA was calculated based on the most recent measurement \( x_n \) multiplied by two. \( f(\text{time}) \times 2 \times x_n \) was now changed in our equation and the fixed point function

\[ 2x_n = a + b \times \exp(c \times \text{time}) \]

is left. The variable of interest is time.

The input of the measurements and the optimization of the parameters used in the equation were implemented using a computer numeric/algebraic standard package, ensuring highest mathematical reliability.

In cases of more than 3 PSA determinations, the system is also able to perform the calculation using more PSA values.

PSA-DT error estimation. The second aspect of our model deals with the minimal and maximal doubling time, depending on the occurrence of measurement errors (PSA interassay, intraassay and biological variability). It is calculated through solving the equation above with different randomly distributed measurement data streams [each variable + chosen range and half range (n=43)] and graphically visualized by plotting major exponential interpolation curves and an interval, where the left boundary is the minimal doubling-time and the right side is the maximum doubling-time depending on an assumed 5-25% PSA variability. In the case of a PSA-DT >10 years, the right boundary is limited to 120 months and is not shown.

The tool was implemented for free access at the following address: http://adam.drahtwarenhandlung.at/webapp/mg2008/chapter_prostata4(example_psa).

The three most recent PSA values (ng/dl) are entered in chronological order. In the last line, PSA variability has to be entered and may be between 5 to 25%. Calculation is then started by clicking on the OK button (Figure 1).

Results

For demonstration, the data for five men with rising PSA after radical prostatectomy were calculated with our tool (PSA-DT and error range) and compared to the results from the Memorial Sloan Kettering Cancer Center (MSKCC) tool (Table I). It has to be emphasized that the results of the MSKCC tool are absolutely correct and just serve as an example to show that different methods lead to different results.

According to our method, the PSA-DT of these 5 men was calculated to be between 1.7 and 15 months (mean: 6.3 months), while with the MSKCC tool it was between 1.3 and 14.5 months (mean: 4.2 months).

Discussion

The wide variation in the natural course of PC represents one of the most challenging problems in its diagnosis and treatment. Therefore, parameters reflecting tumour-aggressiveness are of paramount interest in the management of men with PC. Today, besides histological patterns, the most plausible way to estimate cancer behaviour is using the PSA-DT.

Unfortunately, PSA-DT is not a standardized parameter in current literature, which is mainly due to different
mathematical models for PSA-DT calculation and a lack of standardization regarding input variables for DT calculation. This problem is emphasized by the fact that despite exact definition and reproducibility being fundamental scientific requirements, PSA-DT calculation methodology is not defined in current major guidelines (14, 15).

To overcome this shortcoming in future projects, we propose the following methodology based on a three-step basis: I) PSA-DT calculation using a standardized mathematical method based on a reproducible algebraic standard (MATLAB). II) A defined system of how to handle the input variables (PSA). III) The time interval between single PSA determinations is determined individually according to PSA-DT error estimation.

**Step I:** A variety of mathematical calculation methods can be found in current literature; the so-called 2-point method and the log slope method (1, 11) are widely applied. More sophisticated solutions are, for instance, a random coefficient linear model or a random coefficient quadratic model (12).

Due to the increased influence of data variability of the 2-point method and the lack of evidence to support its equivalence to models such as the log slope method, its use should not longer be recommended (11).

Random coefficient models were described to predict PSA-DT with a high reliability compared to standard methods but do not allow a comparison between different settings and cohorts and cannot be used outside high-volume institutions. Therefore tools such as random coefficient models should not be chosen as the standard method.

Furthermore, as PSA-DT calculation requires computer support, one has to rely on tools that are not always well defined. For instance, the mathematical method applied in the widely used PSA-DT calculator of the MSKCC Center is not described on the homepage (16).

We chose nonlinear optimization based on the least squares error method using the three most recent PSA determinations as proposal for standardized use in every setting and cohort.

**Step II:** For obtaining standardized input variables, we propose to use PSA values which were obtained according to a 5-point rule as outlined in Table II.

Rules are justified as follows: i) Consistency of PSA determination within the same laboratory with the same assay is an indispensable standard in PC diagnosis and follow-up (12). ii) Medical treatment, manipulation, infection or urinary retention may influence PSA values and therefore change the natural course of its increase (14). iii) For standardization purposes, we propose to use the three most recent PSA values, as earlier results may also reflect the early (and eventually linear) increase of PSA (2). iv) Three months between the first and last measurement is the minimum time interval needed to avoid unreliable primary results for PSA-DT error estimation (13, 14). v) Nadir subtraction is not necessary; in contrast to PSA velocity, PSA-DT is a constant parameter and therefore not influenced by this mathematical consideration (2, 3, 11).

In cases where a high number of PSA values over a long period are available, this should be indicated to notify the high level of accuracy (for example when PSA-DT is calculated using 6 values obtained over a period of 18 months, this could be indicated in parentheses after the PSA-DT (6/18 months).

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**Table I. PSA-DT over a period of 3 months in 5 patients with rising PSA after radical prostatectomy, calculated according to our method (plus error range 20 [+10] %) and using the MSKCC tool (1-5=Patient number 1-5).**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/ml)</td>
<td>0.2</td>
<td>0.4</td>
<td>1.0</td>
<td>1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>PSA-DT (months)</td>
<td>15</td>
<td>6</td>
<td>8.9</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Error range (months)</td>
<td>1-120</td>
<td>1.5-12.6</td>
<td>0.1-120</td>
<td>1.1-4.6</td>
<td>0.9-4.7</td>
</tr>
<tr>
<td>MSKCC PSA-DT (months)</td>
<td>9.5</td>
<td>3.7</td>
<td>5.2</td>
<td>1.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

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**Table II. Five-point rule for PSA determination to provide PSA-DT comparability.**

- I All PSA tests carried out in the same laboratory and with the same assay.
- II No medical intervention within the determination interval; no infection, manipulation or urinary retention.
- III Last three PSA values available.
- IV At least three months between the first and last PSA determination.
- V No nadir subtraction after external beam radiation therapy.
Step III: The time interval required to obtain adequate PSA-DT results varies. Serial PSA measurements over a period of one year would provide high PSA-DT accuracy, but this time-span may be too long for routine use. On the other hand, two PSA determinations within three weeks would enable a very fast result to be obtained but leads to a high degree of uncertainty. Estimation of PSA-DT error may guide to an optimal ratio between the time to obtain PSA-DT (as short as possible) and PSA-DT accuracy (as high as necessary). We propose to take three PSA values over a period of three months [as stated in a recent review article (14)] and then check the range of possible PSA-DTs according to the estimation tool. If the range provides sufficient accuracy, a decision can be made; no cut-off value can be discriminated, further determinations should be obtained.

For demonstration purposes, PSA-DT and error estimation in five men with rising PSA after radical prostatectomy were calculated and compared to the results deriving from the MSKCC tool (Table I). The following conclusions might be drawn from this simulation, demonstrating the current and unknown PSA-DT dilemma. Firstly, PSA-DT data generated by different methods are similar but not identical. For instance, the mean PSA-DT differed by 50% between the two tools. This underlines the necessity to use the same method within different cohorts to provide comparability.

Secondly, depending on the different PSA-DT cut-off values, 3 to 12 months in current literature (14, 15, 17, 18), our method resulted in comparable discrimination compared to the MSKCC tool in the majority of examples. Nevertheless, in patients with a relatively long PSA-DT (>6 months), PSA-DT seems inadequately comparable and inaccurate (patient 1 and 3).

Thirdly, according to the calculated error estimation in some cases an adequate result is reached even after a short time of three months. In uncertain cases, an additional PSA determination should be advised within two or three months to increase the accuracy.

For scientific purposes as well as for routine runs, we suggest an adequately defined, open and reproducible PSA-DT calculation and PSA-DT error estimation tool based on standardized PSA data input.

References
16 PSA doubling-time calculator. URL: http://www.mskcc.org/mskcc/html/10088.cfm

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