

THE MATHEMATICAL MODEL FOR PREDICTING THE EARLIEST DIAGNOSTICS PERIOD OF THE SECONDARY DISTANT METASTASES GROWTH PROCESS OF BREAST CANCER



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Aims

Previously, the mathematical models (CoMPaS and CoM-III) of primary tumor (PT) growth and secondary distant metastases (sdMTS) growth of breast cancer (BC) considering TNM classification have been presented (Tyuryumina E., Neznanov A.; 2017, 2018).

Goal: to detect the earliest diagnostics period of visible sdMTS via CoMPaS and CoM-III.

Results

The critical growth periods have been defined via the models CoMPaS and CoM-III:

- 1) the non-visible growth period of PT of BC;
- 2) the non-visible growth period of sdMTS of BC;
- 3) the visible growth period of sdMTS of BC.

The CoMPaS and CoM-III correctly describe the growth period of PT and corresponds to TNM classification (parameter T), the growth period of the sdMTS (parameter M) and the 10-15-year survival of BC patients considering TNM classification.

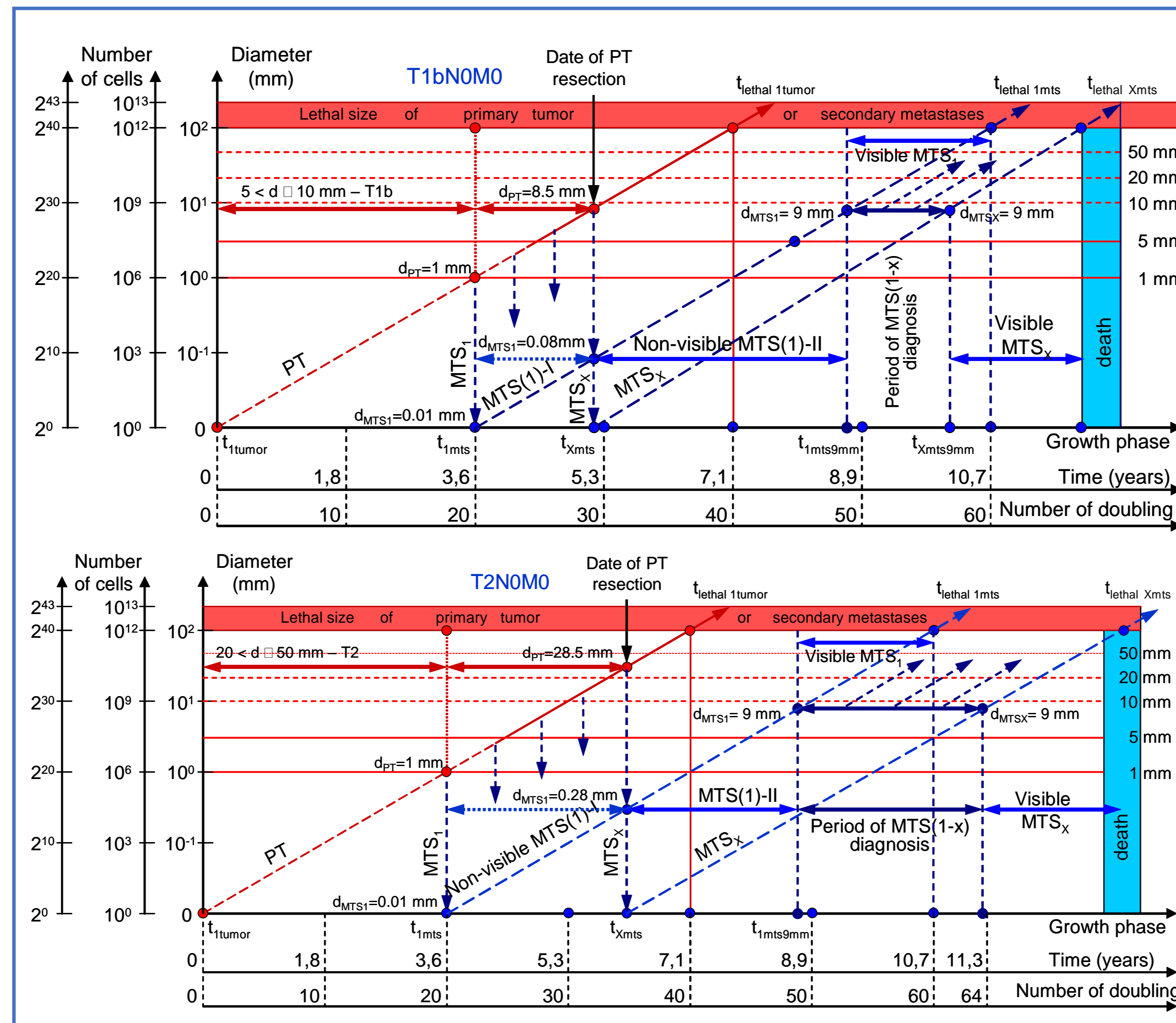
The CoMPaS correctly describes the growth of PT in BC patients with T1-3N0M0 stages and helps to calculate the period in which the sdMTS might appear (M1).

The CoM-III correctly describes the growth of PT in BC patients with T1-3N1-3M0 stages and helps to calculate the period in which the sdMTS might appear (M1).

Conclusions

The models CoMPaS and CoM-III and the corresponded software tool can help:

- 1) to optimise the process of detecting the earliest diagnostics periods of sdMTS in BC patients (T1-3N0-3M0) considering TNM classification and the growth rate of PT and sdMTS of BC;
- 2) to improve the effectiveness of the earliest diagnostics and to start the earliest treatment of small sdMTS in BC patients (T1-3N0-3M0);
- 3) to increase the survival of BC patients with sdMTS (T1-3N0-3M0).



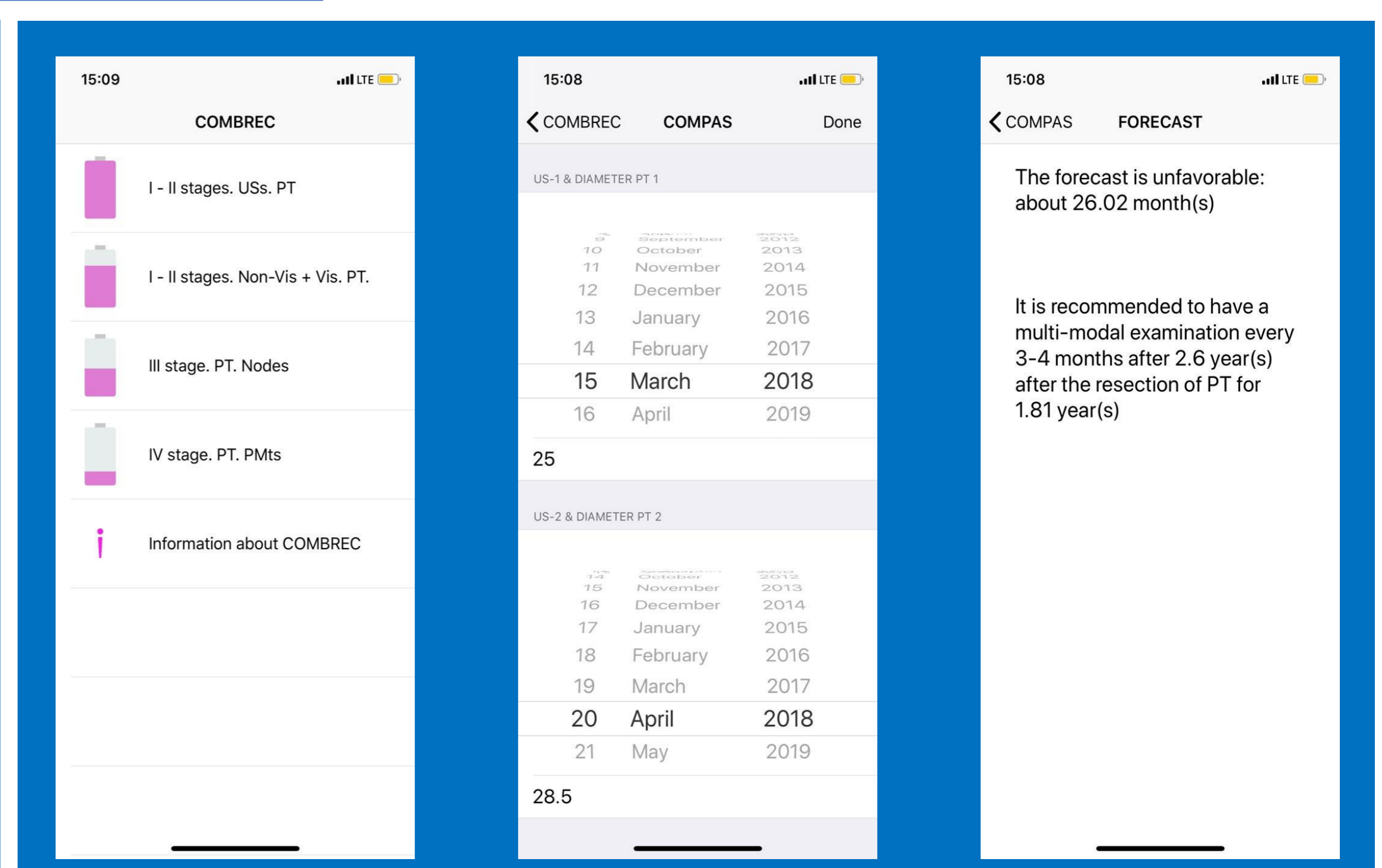
Mathematical model

The models CoMPaS and CoM-III rest on exponential growth model and complementing formulas and correspond to TNM classification. The CoMPaS and CoM-III allow for calculating:

- 1) the tumor volume doubling time (TVDT) of the PT and the sdMTS (CoMPaS);
- 2) the correction coefficient of the sdMTS spreading rate in patients with lymph node MTS related with the PT growth rate (CoM-III);
- 3) the earliest diagnostics periods of the sdMTS.

The CoMPaS model reflects the stages I-II (T1-3N0M0), the growth processes of PT and sdMTS in BC patients without lymph nodes MTS. The CoM-III describes the stages II-III (T1-3N1-3M0), the growth processes of PT and sdMTS in BC patients with lymph nodes MTS.

| | Stage T1-3N0M0 | | | | |
|---------------------------------|-----------------------|------------------------|-------------------------|------------------------|-------------------|
| | T1a (mm) 1 < d ≤ 5 | T1b (mm) 5 < d ≤ 10 | T1c (mm) 10 < d ≤ 20 | T2 (mm) 20 < d ≤ 50 | T3 (mm) d > 50 |
| $pT_{(D)}$ at surgery (mm) | 4.5 | 8.5 | 15.1 | 28.5 | 64.6 |
| $pT_{\log(V)}$ | 26.4 | 29.2 | 31.7 | 34.4 | 38.0 |
| $TVDT_{PT}$ | 70.0 | 70.0 | 70.0 | 65.0 | 60.0 |
| $K_{sMTS(N-)}(N0, n=0)$ | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| $TVDT_{sMTS(N-)}(N0, n=0)$ | 70.0 | 70.0 | 70.0 | 65.0 | 60.0 |
| $sMTS_{\log(V)(N-)}(N0, n=0)$ | 6.44 | 9.19 | 11.68 | 14.43 | 17.97 |
| $sMTS_0(N0, n=0)$ | 0.04 | 0.08 | 0.15 | 0.28 | 0.64 |
| $WNH-PT+MTS(1)$ (years) | 11.5 | 11.5 | 11.5 | 10.7 | 9.9 |
| Total period PT (years) | 5.1 | 5.6 | 6.1 | 6.1 | 6.2 |
| Non-visible PT (years) | 3.8 | 3.8 | 3.8 | 3.5 | 3.3 |
| Visible PT (years) | 1.2 | 1.8 | 2.3 | 2.6 | 3.0 |
| Non-visible MTS(1)-I (years) | 1.2 | 1.8 | 2.3 | 2.6 | 3.0 |
| Non-visible MTS(1)-II (years) | 4.4 | 3.9 | 3.4 | 2.7 | 1.9 |
| Visible MTS(1) (years) | 2.0 | 2.0 | 2.0 | 1.9 | 1.7 |
| Survival MTS(1) (years) | 6.4 | 5.9 | 5.4 | 4.5 | 3.6 |
| $WNH-PT+MTS(x)$ (years) | 12.7 | 13.3 | 13.7 | 13.3 | 12.8 |
| Non-visible MTS(x)-I+II (years) | 5.7 | 5.7 | 5.7 | 5.2 | 4.8 |
| Visible MTS(x) (years) | 2.0 | 2.0 | 2.0 | 1.9 | 1.7 |
| Survival MTS(x) (years) | 7.7 | 7.7 | 7.7 | 7.1 | 6.6 |
| Period of MTS(1-x) diagnosis | 1.2 | 1.8 | 2.3 | 2.6 | 3.0 |



$pT_{(D)}$ at surgery (mm) – the mean size (mm) of the primary tumour at surgery (removal PT).
 $pT_{\log(V)}$ – the number of doublings of the PT at surgery (removal PT).
 $TVDT_{PT}$ – the mean tumour volume doubling time of the PT at surgery (removal PT).
 $K_{sMTS(N-)}(N0, n=0)$ – the mean correcting coefficient of MTS growth rate for N0.
 $TVDT_{sMTS(N-)}(N0, n=0)$ – the mean tumour volume doubling time of secondary distant MTS for N0.
 $sMTS_{\log(V)(N-)}(N0, n=0)$ – the number of doublings of secondary distant MTS at surgery (removal PT) for N0.
 $sMTSD(N0, n=0)$ – the mean size (mm) of secondary distant MTS at surgery (removal PT) for N0.
 $WNH-PT+MTS(1)$ (years) – the whole natural history of the PT and secondary distant MTS growth of breast cancer.
Total period PT (years) – the total period of the PT growth in breast cancer can be calculated as the period from the appearance of the first tumour cell (diameter = 10 μ m) to the pre-surgery size.
Non-visible PT (years) – the non-visible period of PT growth in breast cancer can be calculated as the period from the appearance of the first tumour cell (diameter = 10 μ m) to reaching the visible size (diameter = 1-5 mm) of the PT.
Visible PT (years) – the visible period of PT growth in breast cancer can be calculated as the period from visible size (diameter = 1-5 mm) of the PT to pre-surgery size.
Non-visible MTS(1)-I (years) – the non-visible period of MTS growth can be calculated as the period from the appearance of the first MTS tumour cell (diameter = 10 μ m) to non-visible size of MTS (before the date of PT surgery).
Non-visible MTS(1)-II (years) – the non-visible period of MTS growth can be calculated as the period from diagnosis (after date of PT surgery) to visible size (diameter = 9 mm) of at least one of MTS.
Visible MTS(1) (years) – the visible period of MTS growth can be calculated as the period from diagnoses of the visible size (diameter = 9 mm) to reaching lethal size (death).
Survival MTS(1) (years) – the survival (lifetime) can be calculated as the period between the date of diagnosis (TNM staging system of breast cancer) and the date of patient death. The survival of BC patients included both the non-visible and visible periods of MTS growth.
 $WNH-PT+MTS(x)$ (years) – the whole natural history of the PT and secondary distant MTS growth of breast cancer.
Non-visible MTS(x)-I+II (years) – the non-visible period of MTS growth can be calculated as a period from the appearance of the MTS(x) tumour cell (diameter = 10 μ m) to visible size (diameter = 9 mm) of at least one of MTS.
Visible MTS(x) (years) – the visible period of MTS(x) growth can be calculated as the period from diagnostic of visible size (diameter = 9 mm) to reaching lethal size (death).
Survival MTS(x) (years) – the survival (lifetime) can be calculated as the period between the date of diagnosis (TNM staging system of breast cancer) and the date of patient death. The survival of BC patients included both the non-visible and visible periods of MTS(x) growth.
Period of MTS(1-x) diagnosis – the period of diagnosis of visible size (diameter = 9 mm) of secondary distant MTS from first visible MTS(1) (20th doubling time) to visible MTS(x) (time of removal of the PT).