Consolidated mathematical growth Model of Breast Cancer CoMBreC

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Abstract

This paper is devoted to mathematical modelling of the progression considering stages of breast cancer. Given the relation between primary tumor (PT) and metastases (MTS), the problem of discovering breast cancer (BC) process seems to be twofold: firstly, it is important to describe the whole natural history of BC to understand the process as a whole; secondly, it is necessary to predict the period of a clinical MTS manifestation. In order to understand growth processes of BC on each stage CoMBreC was proposed as a new research tool. The CoMBreC is threefold: CoMPaS (stages I-II), CoM-III (stage III) and CoM-IV (stage IV). A new model rests on exponential growth model and complementing formulas. For the first time, it allows us to calculate different growth periods of PT and MTS in patients with/without lymph nodes MTS: 1) non-visible period for PT; 2) non-visible period for MTS; 3) visible period for MTS. Calculations via CoMBreC correspond to survival data considering stage of BC. It may help to improve predicting accuracy of BC process using an original mathematical model referred to CoMBreC and corresponding software. Consequently, thesis concentrated on: 1) modelling the whole natural history of PT and MTS in patients with/without lymph nodes MTS; 2) developing adequate and precise CoMBreC that reflects relations between PT and MTS; 3) analysing the CoMBreC scope of application. The CoMBreC was implemented to iOS application as a new predictive tool: 1) is a solid foundation to develop future studies of BC models; 2) does not require any expensive diagnostic tests; 3) is the first predictor of survival in breast cancer that makes forecast using only current patient data.

Keywords: breast cancer, exponential growth model, mathematical model, metastases in lymph nodes, mortality, primary tumor, primary metastases, secondary metastases, survival.

1 Introduction

Breast Cancer (BC) is the most common cancer and also the leading cause of cancer mortality in women worldwide. BC accounts for about 20-25% of all cancer types in women [22].

Finding algorithms to predict the growth of tumors has piqued the interest of researchers ever since the early days of cancer research. Many studies were carried out as an attempt to obtain reliable data on the natural history of BC growth.

Mathematical modelling can play a very important role in the prognosis of BC. Various mathematical models were built to describe primary tumor (PT) growth and distant metastases (MTS) growth separately [20].

These days, the exponential, Gompertz, logistic and von Bertalanffy models are included into a group of classical mathematical models of PT growth [1]. For the breast data, the observed linear dynamics were best captured via exponential model that is situated for description of PT growth and, also, for secondary distant MTS growth [8, 9, 11–13, 15–17, 19, 30, 34]. As for Gompertz and logistic models, they are used rarely in order to describe PT growth or secondary distant MTS growth [5, 18, 32].

The duration of the period from the first BC cell to death refers to the natural history of BC [2]. Secondary distant MTS appear in various time in different organs. The interval between resection of PT and the first clinical manifestation of MTS (MTS free survival time or **non-visible** period) determined by PT size, the number of affected lymph nodes and MTS growth rate [3, 5, 8, 9, 12, 13, 15–17, 19, 25, 30, 32–34]. Survival (lifetime) is the period between the date of diagnosis (TNM staging system of BC) and the date of a patient death [22]. Survival among BC patients (%) indicates the percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. The percentage of patients who live at least 5-, 10-, 15-, 20-, 25- and 30-years after PT being treated is defined as 5-, 10-, 15-, 20-, 25- and 30-years observed survival rate of BC patients [22].

It is important to highlight that the natural history of BC continues after resection of PT. The next stage began with secondary distant MTS manifestation. When MTS reach the threshold volume, patients die from process of BC [1, 4, 8, 9, 12, 13, 15–17, 19, 21, 25, 30, 34]. All BC patients get a comprehensive treatment of PT, therefore the *whole natural history of BC* should include the period of growth secondary distant MTS:

1) the **non-visible** period of PT growth;

2) the **visible** period of PT growth, diagnostics and resection of PT;

3) the **non-visible** period of secondary distant MTS growth;

4) the **visible** period of secondary distant MTS growth, diagnostics, treatment and patient's death.

Given the relation between PT and MTS, the problem of discovering BC process seems to be twofold: firstly, it is important to describe the *whole natural history of BC* to understand the process as a whole; secondly, it is necessary to predict the period of a clinical MTS manifestation. Yet, the papers available for this do not offer mathematical growth models of MTS that relate to TNM classification. That leads to the demand building a mathematical model that is based on exponential classical mathematical model, describes *whole natural history of BC* and corresponds to TNM classification. Moreover, the latter aspect of the problem is reflected only by statistical tools that are available as open source. In other words, a patient provides diagnostic data to predictor, and the tool calculates MTS free period and survival according to statistical data. Consequently, it is necessary to create a predictor that makes prognosis of BC for a patient independently from statistical data, and requires no expensive diagnostic data. Thus, this research possesses a novelty since it is the first time the following tools for BC have been proposed: a) *whole natural history of BC*; b) mathematical growth model corresponding to TNM; c) non-statistical software tool for prediction of BC developing.

The **goal** of the research is to improve the prediction accuracy of BC process using the original **Co**nsolidated mathematical growth **M**odel of **Bre**ast **C**ancer (CoMBreC) and implement with model in a software tool.

Practical Value. As it turns out, a new software tool for prediction of BC developing can calculate more accurately: a) MTS free period; b) survival for stages I, II, III, IV of BC including primary MTS and MTS in lymph nodes. Moreover, the predictor can estimate a quality of treatment that was prescribed to a patient. Summarising: CoMBreC a) describes correctly PT growth of stages I, II, III, IV (T1-4N0-3M0-1); b) facilitates the understanding of the appearance period and inception of MTS.

2 Theoretical background

2.1 Pathologic classification of Breast Cancer

To avoid terminological ambiguities, we start with a short introduction into recalling some standard terms such as TNM staging system of BC (Tumor-Node-MTS) and Clinical Classification of Cancer [22] (Tab. 1,2).

Table 1: TNM staging system

Stage	Parameter T	Parameter N	Parameter M
I	T1	N0	M0
II	T1, T2	N0, N1	M0
III	any T	N1, N2, N3	M0
IV	any T	any N	M1

Legend of Table 1:

parameter T	—	size of PT: T1 = 0.1 cm < d ≤ 2 cm; T2 = 2 cm < d ≤ 5 cm; T3 = d > 5 cm; T4 = spread;
parameter N	—	the number of affected lymph nodes: N0: n = 0; N1: n = 1-3; N2: n = 4-9; N3: n = 10-18;
parameter M	—	existence of distant MTS (lungs, bones, liver, etc): M0 = MTS not exist; M1 = MTS exist.

2.2 Tumor doubling time

Moiseenko (2002) [34] detected three following rate options of BC growth:
1) high rate – TDT < 90 days (20%); 2) middle rate – 90 days ≤ TDT ≤ 110 days (60%);
3) low rate – TDT > 110 days (20%).

3 Literature review

3.1 History of mathematical models

Various forms of genetic instability and increased mutation rate can lead to a development of malignancies. At this stage, we can dwell upon a review of classical mathematical growth models of PT and secondary distant MTS of BC, such as the exponential model [4], the von Bertalanffy model [29], the Gompertz model and logistic model [20].

The attempts of PT growth formalisation were pioneered by three different scientists in 1930 independently; namely Casey, Shreck and Mayneord built surface growth and "sigmoid"

Table 2: Clinical Classification of Cancer

Stage 0	T0	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

growth models. I.A. Rodriguez-Brenes et al. [20] provides a complete overview of the history of mathematical models of PT growth.

3.2   Comparative analysis of classical mathematical models of PT growth

V.P. Collins et al. (1956) [4] have proposed that linear exponential growth, determined by measurement of pulmonary MTS and expressed as 'Tumor Volume Doubling Time' (TVDT), is a characteristic of individual cancer, governing the duration before and after diagnosis.

L.Von Bertalanffy (1957) [29] has built a mathematical model, as an attempt to connect metabolism to growth.

A.K. Laird (1964) [14] has introduced an idea that an exact mathematical description of the model of tumor cell proliferation is given by a Gompertz.

J.A. Spratt et al. (1993) [23, 24] have concerned that BC growth rates can be calculated using a form of the logistic equation for a large group of patients undergoing routine screening mammography.

The rate of tumor growth is directly proportional to the tumor size and depends on a number of nutrients.

Concerning that the tumor reaches a maximum size at the certain time, mathematical models, such as Gompertz, von Bertalanffy and logistic, describe a slowing growth rate. Consequently, these models are common S shape (sigmoid curve). A sigmoid curve is a bounded differentiable real function that is defined for all real input values and has a positive derivative at each point [14, 20, 23, 24, 29].

Nowadays, a group of classical mathematical models of PT growth consists of the exponential (with or without free initial volume), Gompertz, logistic and von Bertalanffy models [1]. For data on BC, the observed linear dynamics is best captured by exponential model that is situated for description of PT growth and, also, for secondary distant MTS growth [8, 9, 12, 13, 15–17, 19, 25, 30, 34]. As for Gompertz and logistic, models are used rarely in a description of PT and secondary distant MTS growth processes [5, 18, 32].

I.A. Rodriguez-Brenes et al. (2013) [20] have provided a complete overview of the history of mathematical models of PT growth.

S. Benzekry et al. (2014) [1] have completed the experimental studying about the growth of primary BC and lung cancer. As researchers indicate, both of the Gompertz and exponential growth model describes primary BC most voraciously.

3.3   Mathematical models of secondary distant MTS

After diagnostic of PT, the multi-modality treatment takes place: surgery (lumpectomy, unilateral or bilateral mastectomy), radiotherapy and chemotherapy. Yet, secondary distant MTS appear in different organs, considering the size of PT over time [5]. The metastatic process of tumor cells depends on the number of circulating tumor cells (CTCs) in blood. We may define four levels of CTCs [5]: 1) 0 – almost healthy people; 2) 1-4 tumor cells in 7.5 ml of blood – the lowest level of metastatic process; 3) 5-24 tumor cells – the middle level of metastatic process; 4) more than 25 tumor cells – the most significant level of metastatic process.

The number of CTCs in blood depends on the size of PT, metastatic activity, and tumor cell aggressiveness. The dates of clinical manifestation after resection of PT (i.e. the duration of MTS-free period) is defined by the duration of the pre-clinical non-visible period of BC growth (doubling time) and the metastatic tumor rate [5,6].

Researchers have been actively investigating the problem of formalisation of primary and secondary MTS. Yet, the papers available for this do not offer mathematical models that describe MTS growth relating with TNM classification. Consequently, a new mathematical model ought to be sough to agree with TNM classification, have higher prediction score and be independent from medical statistical parameters.

3.4   Market of BC prediction software

These days prediction of cancer care widely spread from screening to hospice. However, certain predictions problems take place: estimating a probability of appearance PT, a distance between resection PT and appearance secondary MTS, and lifetime for last stages patients. To begin the study, it should be emphasised that many of the early stage cancers induce no symptoms. Therefore, a-propose treatment is recommended in order to increase patient survival. Under such circumstances, recent years have been tend to discover a new way of modelling risk prediction in cancer care. Some studies have also been performed developing statistical prediction algorithms that help evaluate the likelihood of an event personally [31]. At this point, it is important to mention that prediction models:

   a) can demonstrate a greater accuracy than stage forecasting or risk groupings;

   b) can process novel data such as genomic sets;

   c) can suggest treatment methods.

4   Methods

4.1   Consolidated mathematical growth model of *PT* and *secondary MTS* (CoMPaS)

The natural history of BC continues after the resection of PT. Stage I-II (T1-2N0-1M0) means that secondary distant MTS appear after resection of PT [22]. Therefore if MTS reach the

threshold volume, so patients die from progression of BC [1, 4, 8, 9, 12, 13, 15–17, 19, 21, 25, 30, 34].
All of BC patients get the comprehensive treatment of PT, so the whole natural history of BC
should include the period of growth secondary distant MTS (Fig. 1):

1) the **non-visible** period of PT growth (from the appearance of the first tumor cell (diameter = 10 μm) up to reaching of the visible size (diameter = 5 mm) of PT);

2) the **visible** period of PT growth, diagnostics and the resection of PT (from visible size (diameter = 1-5 mm) of PT up to pre-surgery size);

3) the **non-visible** period of secondary distant MTS growth (from diagnosis (date of PT resection) up to visible size (diameter = 5 mm) of at least one of MTS);

4) the **visible** period of secondary distant MTS growth (from diagnostic of visible size (diameter = 5 mm) up to reaching lethal size (death)).
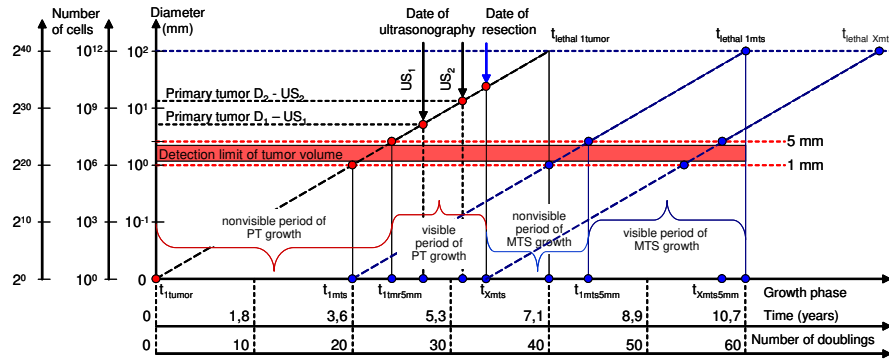

Figure 1: Scheme of the whole natural history of BC [4, 8, 12, 16, 21, 25–28]. As it should be highlighted, the main feature is that model describes PT growth and secondary distant MTS growth as a whole (as indivisible dependent process). Ordinate (Y): Diameter of tumor (mm). Abscissa (X): Time (years). [27, 28]

Legend of Fig. 1 :

t_{1tmr}	—	date of appearance of the first BC stem cell;
$t_{1tmr5mm}$	—	date of appearance of the visible PT with size 5 mm;
$t_{lethal1tumor}$	—	date of appearance of the lethal PT with size 100 mm (when PT reaches the threshold volume);
t_{1mts}	—	date of appearance of the first MTS stem cell that coincides with the period of 20th doubling time;
$t_{1mts5mm}$	—	date of appearance the first visible MTS of breast cancer with size 5 mm;
$t_{lethal1mts}$	—	date of appearance the first lethal MTS of BC with size 100 mm (when secondary distant MTS reaches the threshold volume);
t_{Xmts}	—	date of appearance n_{Xmts} cell of BC MTS that coincides with date of surgery;
$t_{Xmts5mm}$	—	date of appearance n_{Xmts} visible BC MTS with size 5 mm;
$t_{lethalXmts}$	—	date of appearance n_{Xmts} lethal BC MTS with size 100 mm;
US_1	—	date and sizes of the first US of PT;
US_2	—	date and sizes of the second US of PT.

Under such circumstances, description of the whole natural history of BC requires upbuilding
the consolidated mathematical growth model of PT and secondary distant MTS of BC.

It is important to define several admissions (1-3 [1, 8, 9, 11–13, 15, 16, 19, 21, 25, 29, 30, 34]):

1) the exponential growth model was used to describe *natural* growth rate of primary BC;

2) *natural* rate of secondary distant MTS is the same as *natural* growth rate of primary BC;

3) the period of appearance the first metastatic cell of secondary distant MTS coincides with the 20th doubling of primary BC. It allows us to define the *non-visible* growth period of MTS and the initial period of *non-visible* MTS manifestation;

4) *whole nature growth history* of PT and secondary distant MTS is 60 doublings.

The CoMPaS may describe both of PT growth and secondary distant MTS growth considering histopathological classification. Also, the CoMPaS might facilitate the survival (lifetime) and, as a consequence, make predictions of a future metastatic manifestation after the resection of PT [26].

The CoMPaS was designed to predict how cancer is developed [26]. The CoMPaS rests on exponential growth model and consists of nonlinear and linear determined equations $[1, 3, 5, 8, 9, 11–13, 15–17, 19, 21, 25, 29, 30, 33, 34]$ (Fig. 2):

$$
\begin{cases}
\dfrac{dV}{dt} = \dfrac{\log 2}{DT} \ V, \quad t \le DT \ \log_2 \left(\dfrac{\theta \ DT}{log2} \ V_0 \right); \\[3mm]
\dfrac{dV}{dt} = \theta \log \ V, \quad t > DT \ \log_2 \left(\dfrac{\theta \ DT}{log2} \ V_0 \right); \\[3mm]
V(t = 0) = V_0; \\[2mm]
Survival = PT_{\log(V)} + Nonvis_{log} + Vis_{log} \ = \ 60; \\[2mm]
TVDT_{non} = TVDT_{vis} = \dfrac{NonVis_{days} + Vis_{days}}{NonVis_{log} + Vis_{log}};
\end{cases}
$$

|		
$\frac{\log 2}{DT}$	—	the fraction of proliferative cells times;
θ	—	drives the linear phase;
$pT_{\log(V)}$	—	the number of PT doublings;
$Nonvis_{log}$	—	the number of doublings for **non-visible** growth period of MTS;
Vis_{log}	—	the number of doublings for **visible** growth period of MTS;
$TVDT$	—	tumor volume doubling time;
60 doublings	—	the *whole nature growth history* of PT and secondary distant MTS;
DT	$= \dfrac{\log 2 \ (\Delta t)}{\log V_1 - \log V_0}$ [21].	

According to M. Schwartz (1961), the doubling time (DT) can be calculated via the measurement of tumor volume (V_1) at surgery t_1, the first measurement of tumor volume (V_0) at diagnostic t_0 and the period between the measurements (days) ($\Delta t = t_1 \ - \ t_0$) [21].

S. Friberg concerned, the tumor growth rate of BC is constant in visible period of tumor growth, in other words, diameter increases from 1 mm to 100 mm $[1, 3, 5, 8, 9, 11–13, 15–17, 19, 21, 25, 29, 30, 33, 34]$.

The diameter of the first tumor cell equals $10\mu m$. After 10th doubling the diameter of tumor equals 100 μm (the number of cancer cells equals 10^3), after 20th doubling the diameter of tumor equals 1 mm (the number of cancer cells equals 10^6), after 30th doubling the diameter of tumor equals 10 mm (the number of cancer cells equals 10^9), after 40th doubling the diameter of tumor equals 103 mm (the number of cancer cells equals 10^{12}).

The diameter of PT of BC that is more than 10cm (the number of stem cells equals $10^{12} - 10^{13}$), is threshold size of the tumor (lethal size). Such size promote BC patient death $[1, 3, 5, 8, 9, 11–13, 15–17, 19, 21, 25, 29, 30, 33, 34]$. We may define following three tumor growth reasons:

1) the time of cycle dividing proliferating tumor cells;
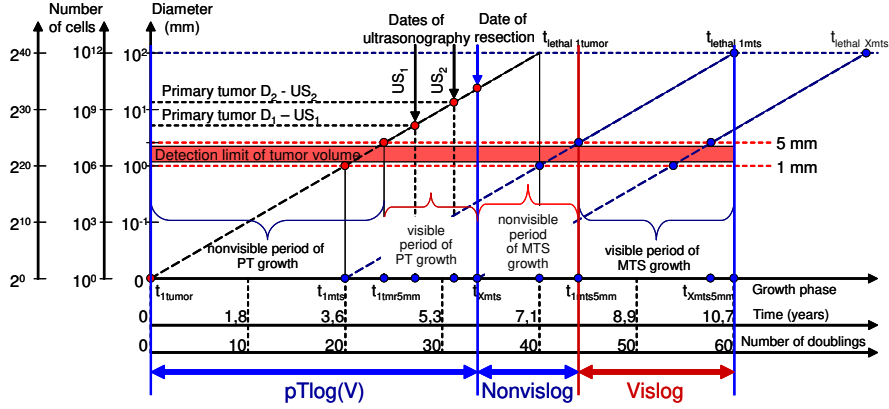
Figure 2:   The first MTS cell appears on the 20th doubling of PT

2) the percentage of proliferation cells;

3) the percentage of spontaneous cell loss in vivo and/or migratory tumor cells.

4.1.1   Limitations

Model does not describe or explain [1, 17, 20]:

- reasons for the lack of secondary MTS (M1) in patients with stage IA, IIA, IIB, (T1-4N0M0) within 25-35 years after resection of PT;

- PT growth with MTS in the regional lymph nodes (T1-4N1-3M0) and primary MTS (T1-4N1-3M1);

4.2   Consolidated mathematical growth model of PT and $primary\ MTS$, IV stage, (CoM-IV)

Stage IV (T1-4N1-3M1) means that secondary distant MTS exist meanwhile PT is growing (M1 - lungs, bones, liver, etc.) [7, 22]. Five-year survival rate of stage IV is about 20-25% among BC patients [10]. Unfortunately, the available papers do not offer a mathematical model that describes stage IV of BC, i.e. the simultaneous growth of PT and primary distant MTS.

We propose a new mathematical growth model for PT and primary MTS. The model may help to improve predicting accuracy of BC process using an original mathematical model referred to CoM-IV and corresponding software [26–28].

The CoM-IV rests on CoMPaS and complementing formulas that describes correcting co-efficient of primary MTS growth rate (K_{pMts}), relating with PT growth rate, tumor volume doubling time of primary MTS ($TVDT_{pMts}$), relating with TVDT of PT [28]:

$$\begin{cases} pMts_{\log(m)} = pT_{\log(V)} - 20; \\ K_{pMts} = \dfrac{pMts_{\log(V)}}{pMts_{\log(m)}}; \\ TVDT_{pMts} = \dfrac{TVDT_{pT}}{K_{pMts}}; \end{cases}$$

$pMts_{\log(m)}$	—	the number of primary MTS doublings, corresponding to IV stage;
$pT_{\log(V)}$	—	the number of PT doublings;
K_{pMts}	—	correcting coefficient of primary MTS growth rate, relating with PT growth rate;
$TVDT_{pMts}$	—	tumor volume doubling time of primary MTS, relating with Tumor volume doubling time of PT ($TVDT_{pT}$);
$pMts_{\log(V)}$	—	the number of primary MTS doublings.

4.2.1 Limitations

Model does not describe or explain [1, 17, 20]:

- reasons for the lack of primary MTS (M1) in patients with stage IA, IIA, IIB, (T1-4N0M0) within 25-35 years after resection of PT

4.3 Consolidated mathematical growth model of *PT* and *secondary MTS* in patients with *MTS in lymph nodes*, III stage, (CoM-III)

Stage III (T1-4N1-3M0) means that lymph nodes MTS (N1-3) exist meanwhile PT (T1-4) is growing [7,22]. Moreover, patients with lymph nodes MTS have higher growth rate of secondary MTS comparing with patients without lymph nodes MTS. Unfortunately, the available papers do not offer mathematical growth models of stage III of BC that cover growth process of PT and secondary MTS in patients with lymph nodes MTS.

We propose a new mathematical growth model for PT and secondary MTS in patients with lymph nodes MTS. The model may help to improve predicting accuracy of BC process using an original mathematical model referred to CoM-III and corresponding software. Consequently, we are interested in: 1) modelling the *whole natural history* of PT and secondary MTS in patients with lymph nodes MTS; 2) developing adequate and precise CoM-III that reflects relations between PT and MTS; 3) analysing the CoM-III scope of application; 4) implementing the model as a software tool.

The CoM-III rests upon CoMPaS and complementing formulas [27]:

$$
\begin{cases}
sMts_{\log(V)(N+)} = pT_{\log(V)} - 20; \\[2mm]
K_{sMts(N+)} = \dfrac{20}{sMts_{\log(V)(N+)} \ \times \ 18 \ \times \ n} + 1; \\[2mm]
TVDT_{sMts(N+)} = \dfrac{TVDT_{pT}}{K_{sMts(N+)}};
\end{cases}
$$

$sMts_{\log(V)(N+)}$	—	the number of doublings of secondary MTS in patients with lymph nodes MTS;
$pT_{\log(V)}$	—	the number of doublings of PT;
20	—	the number of doublings of PT that coincides with the appearance of the first metastatic cell;
$K_{sMts(N+)}$	—	correcting coefficient of secondary MTS of patients with lymph nodes MTS relating with PT growth rate;
n	—	the number of affected lymph nodes (min = 0, max = 18);
$TVDT_{sMts(N+)}$	—	tumor volume doubling time of secondary MTS of patients with lymph nodes MTS relating with tumor volume doubling time of PT ($TVDT_{pT}$).

4.3.1   Limitations

Model does not describe or explain [1, 17, 20]:

- reasons for the lack of MTS in lymph nodes (N1-3) in patients with stage IA, IIA, IIB, (T1-4N0M0) within 25-35 years after resection of PT

5   Results

The CoMBreC was threefold: CoMPaS (stage I-II), CoM-III (stage III), CoM-IV (stage IV). Tab. 3 demonstrates the results of calculations via CoMBreC.

Table 3: Calculations with data from CoMBreC + [6] + [6, 7] + [30]

		T1a	T1b	T1c	T2	T3-4
	CoMPaS					
1	$pT_{(D)}$ at surgery (mm)	4.50	8.50	15.10	28.50	64.60
2	$pT_{\log(V)}$	26.40	29.20	31.70	34.40	38.00
3	$TVDT_{pT}$	70.00	70.00	70.00	65.00	60.00
4	$K_{sMts(N-)}$ (N0, n=0)	1.00	1.00	1.00	1.00	1.00
5	$TVDT_{sMts(N-)}$ (N0, n=0)	70.00	70.00	70.00	65.00	60.00
6	$sMts_{\log(V)}$ (N0, n=0)	6.44	9.19	11.68	14.43	17.97
7	$sMts_D$ (N0, n=0)	0.04	0.08	0.15	0.28	0.64
	CoM-III					
8	$K_{sMts(N+)}$ (N1, n=2)	1.23	1.16	1.12	1.09	1.05
9	$TVDT_{sMts(N+)}$ (N1, n=2)	65.09	64.44	62.37	59.77	56.90
10	$sMts_{\log(V)}$ (N1, n=2)	7.92	10.70	13.11	15.69	18.95
11	$sMts_D$ (N1, n=2)	0.06	0.12	0.21	0.38	0.80
12	$K_{sMts(N+)}$ (N2, n=6)	1.69	1.49	1.37	1.26	1.16
13	$TVDT_{sMts(N+)}$ (N2, n=6)	47.42	50.28	51.21	51.48	51.56
14	$sMts_{(D)}$ (N2, n=6)	0.12	0.24	0.40	0.67	1.25
15	$sMts_{\log(V)}$ (N2, n=6)	10.87	13.71	15.97	18.22	20.91
16	$K_{sMts(N+)}$ (N3, n=14)	2.60	2.15	1.86	1.61	1.38
17	$TVDT_{sMts(N+)}$ (N3, n=14)	30.74	34.93	37.71	40.30	43.42
18	$sMts_{(D)}$ (N3, n=14)	0.48	0.96	1.50	2.17	3.10
19	$sMts_{\log(V)}$ (N3, n=14)	16.77	19.74	21.68	23.28	24.83
	CoM-IV					
20	$K_{pMts(N+)}$ (M1)	4.60	3.20	2.52	2.04	1.64
21	$TVDT_{pMts(N+)}$ (M1)	17.40	23.40	27.80	31.80	36.70
22	$pMts_{\log(V)}$ (M1)	29.40	29.40	29.40	29.40	29.40
23	$pMts_{(D}$ (M1)	9.0	9.0	9.0	9.0	9.0

Legend of Tab. 3:

- TNM parameters depend on PT size: T1, T2, T3, T4, N1, N2, N3, M0, M1 [22]:
- row 1 uses data from tables of paper [7];
- row 2 is calculated from row 1;
- row 3 uses data from figure of paper [10];
- $pT_{(D)}$ means a mean size (mm) of primary tumor at surgery (resection PT);

- $pT_{\log(V)}$ means the number of doublings of PT at surgery (resection PT);
- $TVDT_{pT}$ means a mean tumor volume doubling time of PT at surgery (resection PT);
- $sMts_{(D)}$ means a mean size (mm) of **secondary** distant MTS at surgery (resection PT);
- $sMts_{\log(V)}$ means the number of doublings of **secondary** distant MTS at surgery (resection PT);
- $KsMts$ means a mean correcting coefficient of **secondary** distant MTS growth rate for N1 (n=1-3), N2 (n=4-9), N3 (n=10-18);
- $TVDT_{sMts(N+)}$ means a mean tumor volume doubling time of **secondary** distant MTS for N1 (n=1-3), N2 (n=4-9), N3 (n=10-18);
- $pMts_{(D)}$ means a mean size (mm) of **primary** MTS at surgery (resection PT);
- $pMts_{\log(V)}$ means the number of doublings of **primary** MTS at surgery (resection PT);
- $KpMts$ means a mean correcting coefficient of **primary** MTS growth rate (M1);
- $TVDT_{pMts(N+)}$ means a mean tumor volume doubling time of **primary** MTS growth rate (M1);

For the first time, it was detected that:

- the TVDT of MTS was in range of **62.9** and **68.2** years for pT1, pT2, pT3 considering sizes of PT;

- the TVDT of MTS was in range of **45.7** and **48.1** years for pT4. In other words, the tumor growth aggressively (pT4) considering sizes of PT;

- the *whole natural history* of PT and MTS growth (the period from the appearance of the first tumor cell up to death) was in range of **10.3** and **11.2** years for pT1, pT2, pT3 (Fig. 3);

- the *whole natural history* of PT and MTS growth (the period from the appearance of the first tumor cell up to death) was in range of **7.5** and **7.9** years for pT4.
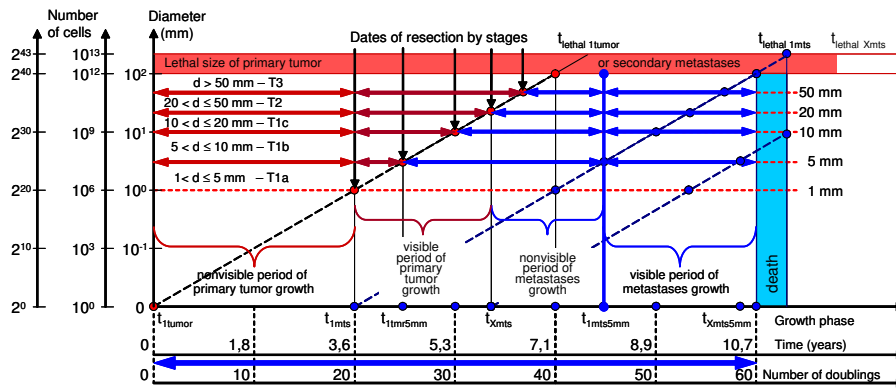

Figure 3: The whole natural history of PT growth – from the appearance of the first tumor cell up to death – in range of 10.3 and 11.2 years for pT1, pT2, pT3

The survival of BC patients included both of the **non-visible** and **visible** periods of MTS growth whereas **non-visible** was the period from date of resection PT to date of diagnostic of secondary distant MTS 5-10 mm (MTS free period), **visible** was the period from date of diagnostic of secondary distant MTS 5-10 mm to the death of patient BC.

For the first time, it was detected that the survival was in range of **2.9** to **3.0** years for pT1, pT2, pT3 (Fig.3).

Non-visible and **visible** periods of MTS growth whereas **non-visible** was the period from date of resection PT to date of diagnostic of secondary distant MTS 5-10 mm (MTS free period), **visible** was the period from date of diagnostic of secondary distant MTS 5-10 mm to the death of patient BC.

For the first time, it is possible to calculate an approximate period of appearance of the first MTS cell considering size PT (parameter T) for pT1, pT2, pT3.

For the first time, it was detected that the sizes of secondary distant MTS was in range of **0.08** and **0.64** mm at date of resection PT. In other words, the size of secondary distant MTS was lower than 1 mm (the minimum size for diagnostic of tumor), consequently, secondary distant MTS could not be detected (Fig. 4).
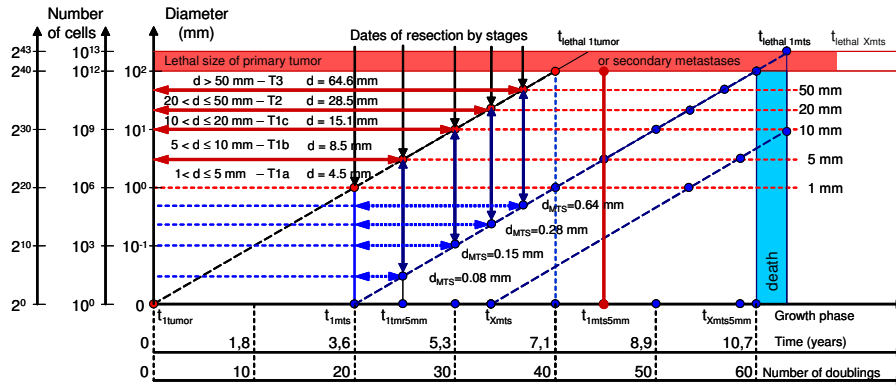
Figure 4: Size of secondary distant metastases was in range of 0.08 mm and 0.64 mm at surgery date (diameter below diagnostic level).

For the first time, it was detected that:

- the **non-visible** period of MTS growth was in range of **1.9** to **3.2** years for pT1, pT2, pT3;

- the **visible** period of MTS growth was in range of **1.9** to **2.1** years for pT1, pT2, pT3;

- the **visible** period of MTS growth was in range of **1.8** to **1.9** years for pT4. In other words, the **visible** period of MTS growth for **pT4** almost equalled the **visible** period of MTS growth for **pT1, pT2, pT3**.

The CoMBreC describes correctly PT and primary distant MTS growth T1-4N0-3M1 – stage IV with (N1-3) or without MTS in lymph nodes (N0) (Fig. 5).

The CoMBreC describes correctly T1-4N1-3M1 – stage IV the period of PT growth considering TNM classification (parameter T).
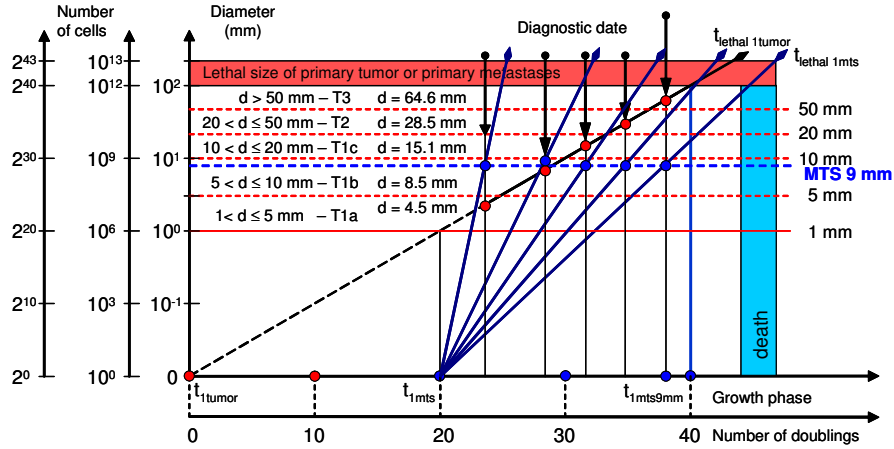

Figure 5: Whole natural history of PT and primary distant MTS of patients with BC (IV stage). Parameter T (T1a: 1 mm < d ≤ 5 mm; T1b: 5 mm < d ≤ 10 mm; T1c: 10 mm < d ≤ 20 mm; T2: 20 mm < d ≤ 50 mm; T3: d > 50 mm; T4: d = any). Parameter N (N0: n=0; N1: n=1-3; N2: n=4-9, N3: n=10) – affected lymph nodes. Parameter M (M1) – distant primary MTS.

For the first time, considering H.R. Withers [33], the CoMBreC allowed us to calculate the variety of correcting coefficients of an increase:

1) the growth rate of **secondary** distant MTS relating with the growth rate of PT considering stage and sizes of PT (parameter T - pT1a, pT1b, pT1c, pT2, pT3-4) and the number of affected lymph nodes (parametr N, stage III);

2) the growth rate of **primary** distant MTS relating with the growth rate of PT considering stage and sizes of PT (parameter T - pT1a, pT1b, pT1c, pT2, pT3-4).

The CoMBreC demonstrated changes of the growth rate of **secondary** distant MTS relating with the growth rate of PT considering stage and sizes of PT (parameter T - pT1a, pT1b, pT1c, pT2, pT3-4) and the number of affected lymph nodes (parametr N, stage III).

The CoMBreC for T1aN0-3M0-1 (Fig. 6): T1aN0M0 (stage I) , T1aN1M0 (stage II) , T1aN2-3M0 (stage III) , T1aN0-3M1 (stage IV).
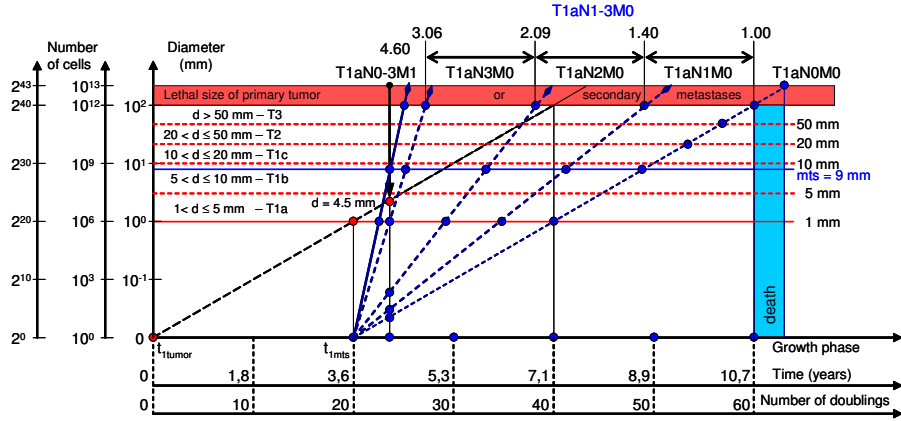

Figure 6: T1aN0-3M0-1. The *whole natural history* of PT and secondary distant MTS for BC patients. Parameter T (T1a: 1 mm < d ≤ 5 mm) – diameter of PT. Parameter N (N0: n=0; N1: n=1-3; N2: n=4-9, N3: n=10-18) – affected lymph nodes. Parameter M (M0: no evidence of distant MTS; M1: distant detectable MTS).

The CoMBreC for T1bN0-3M0-1 (Fig. 7): T1bN0M0 (stage I) , T1bN1M0 (stage II) , T1bN2-3M0 (stage III), T1bN0-3M1 (stage IV).
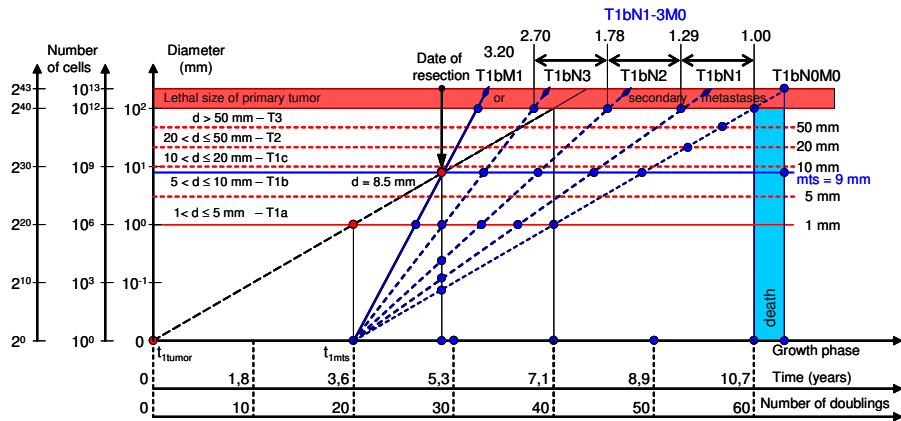

Figure 7: T1bN0-3M0-1. The *whole natural history* of PT and secondary distant MTS for BC patients. Parameter T (T1b: 5 mm < d ≤ 10 mm) – diameter of PT. Parameter N (N0: n=0; N1: n=1-3; N2: n=4-9, N3: n=10-18) – affected lymph nodes. Parameter M (M0: no evidence of distant MTS; M1: distant detectable MTS).

The CoMBreC for T1cN0-3M0-1 (Fig. 8): T1cN0M0 (stage I) , T1cN1M0 (stage II) , T1cN3M0 (stage III), T1cN0-3M1 (stage IV).
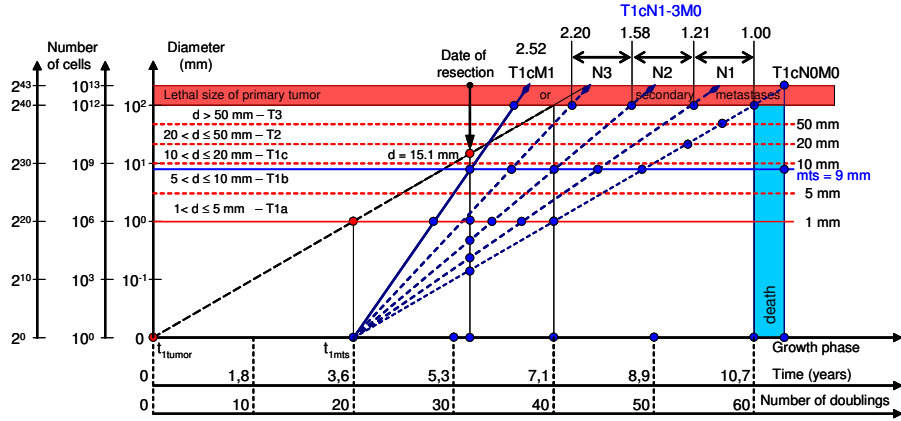

Figure 8: T1cN0-3M0-1. The *whole natural history* of PT and secondary distant MTS for BC patients. Parameter T (T1c: 10 mm < d ≤ 20 mm) – diameter of PT. Parameter N (N0: n=0; N1: n=1-3; N2: n=4-9, N3: n=10-18) – affected lymph nodes. Parameter M (M0: no evidence of distant MTS; M1: distant detectable MTS).

The CoMBreC for T2N0-3M0-1 (Fig. 9): T2N0-1M0 (stage II), T2N2-3M0 (stage III), T2N0-3M1 (stage IV).
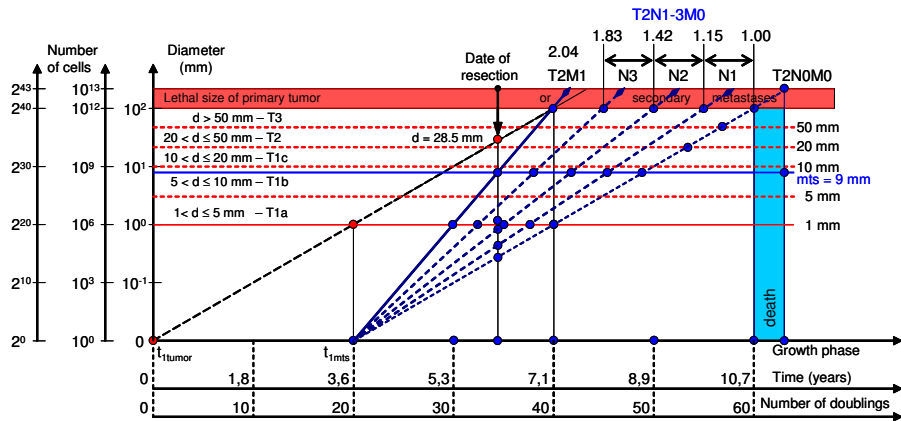

Figure 9: T2N0-3M0-1. The *whole natural history* of PT and secondary distant MTS for BC patients. Parameter T (T2: 20 mm < d ≤ 50 mm) – diameter of PT. Parameter N (N0: n=0; N1: n=1-3; N2: n=4-9, N3: n=10-18) – affected lymph nodes. Parameter M (M0: no evidence of distant MTS; M1: distant detectable MTS).

The CoMBreC for T3N0-3M0-1 (Fig. 10): T3N0M0 (stage II), T3N1-3M0 (stage III), T3N0-3M1 (stage IV).
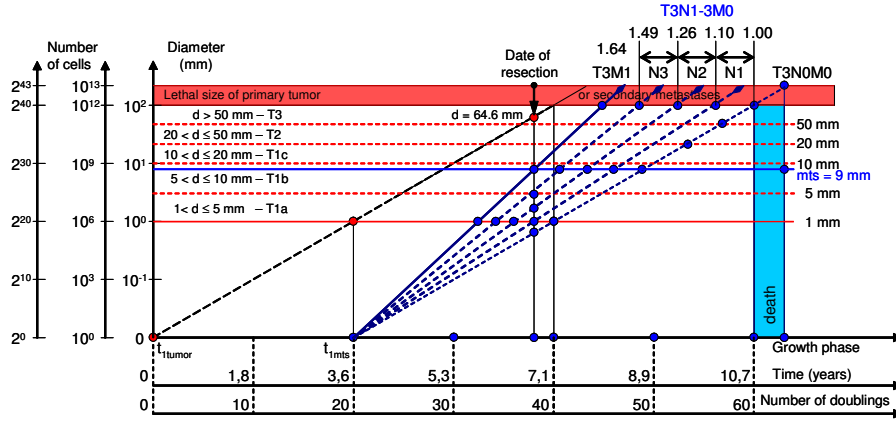

Figure 10: T3N0-3M0-1. The *whole natural history* of PT and secondary distant MTS for BC patients. Parameter T (T3: 50 mm < d) – diameter of PT. Parameter N (N0: n=0; N1: n=1-3; N2: n=4-9, N3: n=10-18) – affected lymph nodes. Parameter M (M0: no evidence of distant MTS; M1: distant detectable MTS).

6   Software tool for prediction BC developing

At this stage, it is relevant to shed light on predictor specifications. We implement the CoMPaS, CoM-III and CoM-IV as a software tool. The application is build using Swift and referred as CoMBreC.

AppStore Application Description

Developer	Ella Tyuryumina
Category	Medicine
Updated	5.04.2017
Version	2.0
Size	29 MB
Compatibility	Requires iOS 10+
Compatible with	iPhone
	and iPod touch
Languages	English
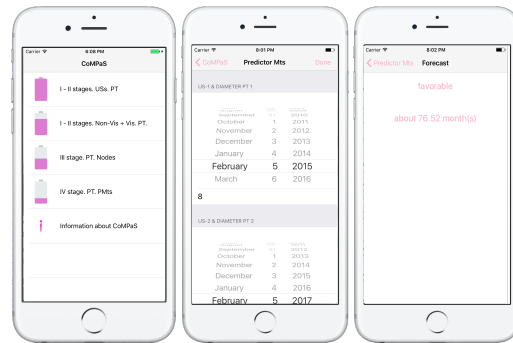
INPUT DATA:

- the first ultrasound diagnostic data:

    – date
    – diameter (mm)

- the second ultrasound diagnostic data:

    – date
    – diameter (mm)
    – * diameter of primary MTS (for CoM-IV)

- * the number of affected lymph nodes (n) (for CoM-III)

OUTPUT DATA:

- forecast:

    – the number of months

    – category of forecast:

        * favorable
        * mid-favorable
        * unfavorable

The **CoMPaS** model and predictive software:

1) allow us to detect different growth periods of PT and **secondary** distant MTS growth in patients **without** lymph nodes MTS;

2) allow us to make forecast of the period of **secondary** distant MTS manifestation in patients **without** lymph nodes MTS;

3) have higher average prediction accuracy than the other tools;

4) can improve forecasts on survival of BC and facilitate optimisation of diagnostic tests.

The **CoM-III** model and predictive software:

1) allow us to detect different growth periods of PT and **secondary** distant MTS growth in patients **with** lymph nodes MTS;

2) allow us to make forecast of the period of **secondary** distant MTS manifestation in patients **with** lymph nodes MTS;

3) have higher average prediction accuracy than the other tools;

4) can improve forecasts on survival of BC and facilitate optimisation of diagnostic tests.

The **CoM-IV** model and predictive software:

1) allow us to detect different growth periods of PT and **primary** distant MTS growth;

2) allow us to make forecast of the period of **primary** distant MTS manifestation;

3) have higher average prediction accuracy than the other tools;

4) can improve forecasts on survival of BC and facilitate optimisation of diagnostic tests.

It is necessary to collect predictions in one database to compare forecasts with real data and estimate effectiveness of proposed model. Consequently, the CoMPaS connects to database that allows to test application and model.

As it turns out, the new predictive tool: 1) is a solid foundation to develop future studies of BC models; 2) does not require any expensive diagnostic tests; 3) is the first predictor that makes forecast using only current patient data, whilst the others are based on the additional statistical data.

7   Discussion

Considering previous studies, the growth rate of primary MTS in BC patients with stage T1-4N1-3M1 (parameter M1 - stage IV) should be higher than natural growth rate of PT [4–7, 9, 10, 13, 15, 21, 22].

S. Koscielny et al. (1985) [12] have showed the growth rate of secondary distant MTS is higher than the natural growth rate of PT 2.2 times.

M. Tubiana et al. (1989) [25] have proposed that growth rate of secondary distant MTS of BC could have low and high growth rate. Consequently, growth rate of secondary distant MTS of BC could be equal or higher than the natural growth rate of PT .

H.R. Withers et al. (2006) [33] have provided an attempt of summarising data of the growth rate of secondary distant MTS and building growth model of secondary distant MTS.

The unique CoMBreC described parameters of BC (T,M,N) according the TNM classification, Fig. 6 - 10. As it should be highlighted, the calculations via CoMBreC corresponded to 10-15 years survival of BC patients. In other words, CoMBreC covers all stages in terms of description growth and prediction development of BC growth process (Tab 4).

Table 4: Clinical Classification of Cancer

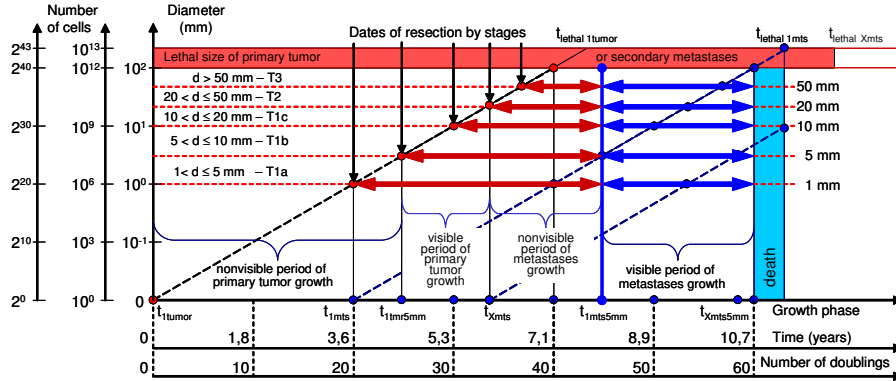| Stage	T	N	M	Model
Stage I	T1	N0	M0	CoMPaS
Stage IIA	T0	N1	M0	CoM-III
	T1	N1	M0	CoM-III
	T2	N0	M0	CoMPaS
Stage IIB	T2	N1	M0	CoM-III
	T3	N0	M0	CoMPaS
Stage IIIA	T0	N2	M0	CoM-III
	T1	N2	M0	CoM-III
	T2	N2	M0	CoM-III
	T3	N1, N2	M0	CoM-III
Stage IIIB	T4	N0	M0	CoMPaS
	T4	N1	M0	CoM-III
	T4	N2	M0	CoM-III
Stage IIIC	Any T	N3	M0	CoM-III
Stage IV	Any T	Any N	M1	CoM-IV

Figure 11: Survival includes the non-visible growth period and the visible growth period of secondary distant MTS.

Relative survival (%) of patients with BC depends on diameter of PT (T parameter) (Fig. 12), whereas survival (lifetime) means the period between the date of diagnosis (TNM staging system of BC) and the date of a patient death [28-30].

Relative survival (%) of patients with BC: 1) depends on *non-visible* growth period of MTS (MTS free period); 2) do not depend on *visible* growth period of MTS from the first metastasising up to the date of a patient death (Fig. 12).

For the first time, the CoMBreC allowed us to understand the phenomena of differences between 15-years (considering diameter PT) survival and 10-years survival of BC patients (considering date of MTS manifestation) Fig. 12.

The survival included the *non-visible* period and the *visible* period of secondary distant MTS. In other words, the survival period was from date of diagnostic secondary distant MTS (5-10 mm) to date of death patient BC (Fig. 6-10,12).

The analysis of *non-visible* growth period of the secondary distant metastases of breast cancer helps to consider the cause of differences between 10-15-years mortality of breast cancer patients considering the breast cancer stage (parameter M) (Fig. 6-10,12) [26–28]. It is important to mention that the CoMBreC could be used as the standard of estimation the effectiveness of prescribed treatment to a patient BC. In other words, if survival of a patient increases, so the treatment has a positive effect. And vice-versa, if survival of a patient decreases, so the treatment has a negative effect. Consequently, the personalised approach of treatment allows us to increase effectiveness of prescribed treatment to a patient.

The proposed data indicated usage opportunities of the CoMBreC for analysis of real patient data and comparing with statistical data from open sources.

8   Conclusion

The analysis of modern state of BC included 34 papers. Meta-analysis of the clinical data showed that growth process of MTS depends on growth process of PT. Given the relation between PT and MTS, the *whole natural history of BC* was described for each stage to understand the growth process of BC as a whole, so it allowed us to predict the period of a clinical manifestation of MTS relating to TNM classification. Thus, it was the first time the following were proposed for BC: a) mathematical growth model corresponding to TNM (CoMBreC); b)

non-statistical software tool for prediction of BC developing.

The "**C**onsolidated mathematical growth **M**odel of **Bre**ast **C**ancer" (CoMBreC) improved the prediction accuracy of BC process by detecting growth periods of PT and MTS for patients with/without lymph nodes. As a consequence, the CoMBreC allowed us to estimate the quality of treatment according to the *whole natural history* data and patient's survival data. For the first time:

1. The CoMPaS allowed us to calculate:

   - the number of doublings for **non-visible** growth period of secondary distant MTS;
   - the number of doublings for **visible** growth period of secondary distant MTS;
   - tumor volume doubling time (days) for **non-visible** growth period of secondary MTS;
   - tumor volume doubling time (days) for **visible** growth period of secondary MTS.

2. The *whole natural history* of PT and secondary distant MTS growth was build considering stages (pT1, pT2, pT3 and pT4) and pT sizes.

3. The CoM-III allowed us to:

   - calculate correcting coefficients of the growth rate of secondary distant MTS (parameter N1-3, stage III) considering stage (pT1, pT2, pT3 and pT4) and pT sizes;
   - show variety of the growth rate of secondary distant MTS (parameter N1-3, stage III) considering stage (pT1, pT2, pT3 and pT4) and pT sizes;
   - build *whole natural history* of PT and secondary distant MTS growth considering PT sizes.

4. The CoM-IV allowed us to:

   - calculate correcting coefficients of the growth rate of primary distant MTS (parameter M1, stage IV) considering stage (pT1, pT2, pT3 and pT4) and pT sizes;
   - show variety of the growth rate of primary distant MTS (parameter M1, stage IV) considering stage (pT1, pT2, pT3 and pT4) and pT sizes;
   - build *whole natural history* of PT and primary distant MTS growth considering PT sizes.

5. The CoMBreC was implemented as a software tool via mean values from calculations.

6. The CoMBreC was created to help to model different clinical stages of BC (I, II, III and IV) corresponding to TNM classification and to predict 10-years survival of BC patients.

9   Theoretical Value

1. Built the consolidated mathematical growth model of **primary tumor** and **secondary distant metastases** of breast cancer in patients **without** lymph nodes metastases, T1-4N0M0, stage I-II, (**CoMPaS**).

2. Determined the critical growth periods of **primary tumor** and **secondary distant metastases** of breast cancer to predict survival of patients with breast cancer (CoMPaS).

3. Built the consolidated mathematical growth model of **primary tumor** and **secondary distant metastases** of breast cancer in patients **with** lymph nodes metastases, T1-4N1-3M0, stage III, (**CoM-III**).

4. Built the consolidated mathematical growth model of **primary tumor** and **primary distant metastases** of breast cancer, T1-4N0-3M1, stage IV, (**CoM-IV**).

5. Built the original consolidated mathematical growth model of **primary** tumor, **primary** and **secondary** distant metastases of breast cancer (**CoMBreC**):

   • to describe different clinical stages of breast cancer (I, II, III and IV) corresponding to TNM-classification;

   • to predicts the 10-years survival of patients with breast cancer.

10   Practical Value

The **CoMBreC**:

1. The **CoMPaS**

   • was built to predict breast cancer process on stage I-II;

   • rested on exponential tumor growth model and consists of a system of determinate nonlinear and linear equations;

   • described correctly primary tumor growth (parameter T1-4) and secondary distant metastases growth (parameter M0) in patients without lymph nodes metastases (parameter N0);

   • determined different growth periods of primary tumor and secondary distant metastases that was not possible beforehand:

      – **non-visible** growth period of primary tumor;
      – **non-visible** growth period of secondary metastases;
      – **visible** growth period of secondary metastases.

   • corresponded to data of 10-15-year survival in patients with the different tumor stage;

   • facilitated understanding the differences between the **nonvisible** growth period of MTS and 15-year survival considering tumor stage.

2. The **CoM-III**

   • was built to predict breast cancer process on stage III;

   • rested on CoMPaS and complementing formulas;

   • described correctly primary tumor growth (parameter T1-4) and secondary distant metastases growth (parameter M0) in patients with lymph nodes metastases (parameter N1-3);

   • determined different growth periods of primary tumor and secondary distant metastases considering the number of affected lymph nodes:

      – **non-visible** growth period of primary tumor;
      – **non-visible** growth period of secondary metastases;

– **visible** growth period of secondary metastases.

- corresponded to data of 10-15-year survival in patients with the different tumor stage;
- facilitated understanding the differences between the **nonvisible** growth period of MTS and 15-year survival considering tumor stage.

3. The **CoM-IV**

- was built to predict breast cancer process on stage IV;
- rested on CoMPaS and complementing formulas;
- described correctly primary tumor growth (parameter T1-4) and secondary distant metastases growth (parameter M1) in patients with/without lymph nodes metastases (parameter N0-3);
- determined different growth periods of primary tumor and primary distant metastases:
  – **non-visible** growth period of primary tumor;
  – **non-visible** growth period of primary metastases;
  – **visible** growth period of primary metastases.
- corresponded to data of 10-15-year survival in patients with the different tumor stage;
- facilitated understanding the differences between the **nonvisible** growth period of MTS and 15-year survival considering tumor stage.

4. Software tool via CoMBreC:

- can calculate more accurately MTS free period;
- survival for stages I, II, III, IV of BC considering primary MTS and lymph nodes MTS;
- can estimate a quality of treatment that was prescribed to a patient.

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