ICHI 2017

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Edited by Christophe Giraud-Carrier, Julio Facelli, Hiroshi Nakajima, Mollie Cummins, Gerrit Meixner

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Welcome to IEEE ICHI 2017!

The IEEE International Conference on Healthcare Informatics (ICHI) series is the premier community forum concerned with the application of computer science principles, information science principles, information technology, and communication technology to address problems in healthcare, public health, and everyday wellness. It serves as a venue for discussion of innovative technical and empirical approaches, highlighting end-to-end applications, systems, and technologies, even if available only in prototype form, as well as related social and ethical implications.

The Fifth IEEE International Conference on Healthcare Informatics (ICHI 2017) took place in Park City, Utah, in the heart of the Rocky Mountains, from August 23rd to August 26th, 2017.

As in the past, the conference featured a number of keynote addresses from renowned researchers and practitioners, a multi-track technical and industry program including oral presentations and poster sessions, a panel featuring relevant agencies and foundations funding research in this area, specialized workshop and tutorials, and a doctoral consortium.

The call for papers attracted 117 submissions from 25 different countries along 3 main tracks: Human Factors, Systems, and Analytics. In addition, 11 poster submissions were received (as abstracts only). All submissions were peer-reviewed for relevance, technical soundness, originality, and overall quality. 31 papers were selected for oral presentations (27% acceptance rate), and presented in 6 non-overlapping sessions. Another 40 papers were selected for poster presentations (61% acceptance rate). Finally, 7 of the 11 poster/abstract-only submissions were also accepted. To ensure lively poster sessions, rapid-fire sessions were introduced this year giving each poster presenter 1 minute/1 slide to highlight their work in a short plenary session preceding their poster session.

The scientific tracks were complemented by an industry track featuring 2 poster presentations and 4 guest speakers from very large healthcare companies; a panel comprising representatives from the National Science Foundation, the National Institutes of Health, and the Robert Wood Johnson Foundation discussed funding opportunities; and a doctoral consortium that attracted 8 doctoral students who were able to present a poster of their research and receive individual feedback.

We are most grateful to our Program Committee consisting of over 70 members from 19 countries for their tireless work in providing meaningful and constructive reviews, selecting, and organizing papers, tutorials and workshops. We also express appreciation to our Keynote and Invited Speakers for graciously accepting our invitations, and kindly sharing their experience and expertise with the ICHI 2017 community. We are indebted to our sponsors, both corporate and government, for their financial support, including travel grants to 15 students. Finally, we express our thanks to the staff at Brigham Young University's Conferences and Workshops for their invaluable logistics support throughout.

We hope you enjoy the material found in these Proceedings, and look forward to seeing you again next year!

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On Consolidated Predictive Model of the Natural History of Breast Cancer Considering Primary Tumor and Primary Distant Metastases Growth

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***Abstract*—We propose a new mathematical growth model of primary tumor and primary metastases which may help to improve predicting accuracy of breast cancer process using an original mathematical model referred to CoM-IV and corresponding software. The CoM-IV model and predictive software: a) detect different growth periods of primary tumor and primary metastases; b) make forecast of patient survival; c) have higher average prediction accuracy than the other tools; d) can improve forecasts on survival of BC and facilitate optimisation of diagnostic tests. The CoM-IV enables us, for the first time, to predict the whole natural history of primary tumor and primary metastases growth on each stage (pT1, pT2, pT3, pT4) considering only on primary tumor sizes. Summarising: CoM-IV a) describes correctly primary tumor and primary distant metastases growth of IV (T1-4N0-3M1) stage with (N1-3) or without regional metastases in lymph nodes (N0); b) facilitates the understanding of the appearance period and manifestation of primary metastases.**

***Index Terms*—breast cancer; exponential growth model; mathematical model; primary tumor; primary metastases; survival**

I. 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 [1].

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 modeling 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 [2].

These days, the exponential, Gompertz, logistic and von Bertalanffy models are included into a group of classical mathematical models of PT growth [3]. For the breast data, the observed linear dynamics were best captured by exponential model, which is situated for description of PT growth and, also, for secondary distant MTS growth [4]–[14]. As for Gompertz and logistic models, they are used rarely in order to describe PT growth or secondary distant MTS growth [15]–[18].

The duration of the period from the first BC cell to death refers to the natural history of BC [19]. secondary distant MTS appear in various time in different organs. The interval between removal of PT and the first clinical manifestation of MTS (MTS free survival time or nonvisible period) determined by PT size, the number of affected lymph nodes and MTS growth rate [4]–[8], [10]–[14], [16]–[18], [20]–[22]. Survival (lifetime) is the period between the date of diagnosis (TNM staging system of BC) and the date of a patient death [1]. 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 being treated PT is defined as 5-, 10-, 15-, 20-, 25- and 30-years observed survival rate of BC patients [1], [16].

Various forms of genetic instability and increased mutation rate can lead to a development of malignancies. I.A. Rodriguez-Brenes et al. [2] provides a complete overview of the history of mathematical models of PT growth. Nowadays, as I.A. Rodriguez-Brenes concerned, 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 [3]. For the breast data, 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 [4]–[8], [10]–[14], [20]. As for Gompertz and logistic, models are used rarely in a description of PT and secondary distant MTS growth processes [15]–[18].

S. Benzekry et al. (2014) [3] has 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.

Unfortunately, the available papers for this do not offer mathematical models which 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 statistical parameters.

It is important to highlight that the natural history of BC continues after removal of PT. The next stage began with

secondary distant MTS manifestation. When the MTS reach the threshold volume, patients die from process of BC [3]–[8], [10]–[14], [16], [20], [23], [24]. All BC patients get a comprehensive treatment of PT, so the *whole natural history of BC* should include the period of secondary distant MTS growth:

1) the **nonvisible** period of PT growth;
2) the **visible** period of PT growth, diagnostics and removal of PT;
3) the **nonvisible** period of secondary distant MTS growth;
4) the **visible** period of secondary distant MTS growth, diagnostics, treatment and patient's death.

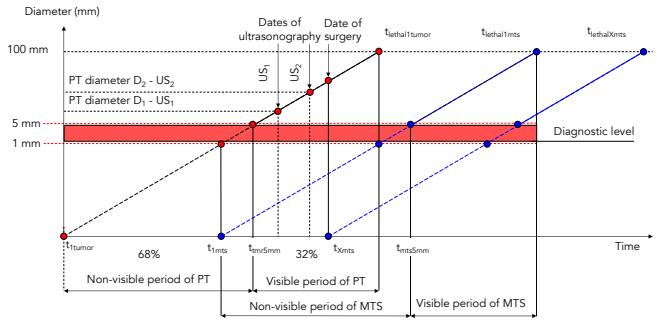

Fig. 1. Scheme of the whole natural history of BC (stage I-II) [10], [12], [13], [20], [23], [24]. As it should be highlighted, the main feature is that model describes PT growth and secondary distant MTS growth as a whole (as indivisible dependent process).
Ordinate (Y): Diameter of tumor (mm). Abscissa (X): Time (years).

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, which coincides with the period of 20^{th} 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 nXmts cell of BC MTS, which coincides with date of surgery;
$t_{Xmts5mm}$	—	date of appearance nXmts visible BC MTS with size 5 mm;
$t_{lethalXmts}$	—	date of appearance nXmts 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.

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 available papers for this do not offer mathematical growth models of MTS that relate to TNM classification. That leads to the demand of building a mathematical model that rests 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 forecast for 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 treatment 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.

To avoid terminological ambiguities, we dwell upon recalling some standard terms and TNM classification of BC (Tumor-Node-MTS) [1].

TABLE I
TNM STAGING SYSTEM

Stage	Parameter T	Parameter N	Parameter M
I	T1	N0	M0
II	T1, T2	N0, N1	M0
III	T1, T2, T3, T4	N1, N2, N3	M0
IV	any T	any N	M1

Legend of Table 1:

parameter T	—	size of PT: T1 = 0.1 d $\leq$ 2 cm; T2 = 2 d $\leq$ 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;
parameter M	—	existence of distant MTS (lungs, bones, liver, etc): M0 = MTS not exist; M1 = MTS exist.

The **goal** of the research is to improve the prediction accuracy of BC process, using the original **Co**nsolidated mathematical growth **M**odel of primary tumor and primary metastases (CoM-IV). To make precise the scope of the study it is necessary to fulfil several **tasks**:

1. To model the *whole natural history* of PT and MTS for stage IV;
2. To develop adequate and precise CoM-IV which reflects relations between PT and primary MTS building Consolidated mathematical growth model for *PT* and *primary MTS*, IV stage, (**CoM-IV**);
3. To analyse the CoM-IV scope of applications;
4. To implement the model as 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 stage IV of BC including

primary MTS and primary MTS. Moreover, the predictor can estimate a quality of treatment which was prescribed to a patient. Summarising: CoM-IV a) describes correctly PT and primary distant MTS growth of IV (T1-4N0-3M1) stage with (N1-3) or without regional metastases in lymph nodes (N0); b) facilitates the understanding of the appearance period and manifestation of primary MTS.

II. Materials and Methods

***Co**nsolidated mathematical growth **M**odel of **PT** **a**nd secondary MT**S**, I-II stages, (**CoMPaS**)*

In 2015 we proposed a consolidated mathematical growth model of PT and secondary MTS (CoMPaS) that describes correctly PT growth (parameter T) as well as secondary MTS growth (parameter M), corresponds to TMN [25], [26]. Also, the CoMPaS might facilitate the survival (lifetime) and, as a consequence, make predictions of a future metastatic manifestation after removal of the PT.

It is important to define several admissions (1-3 [3]–[13], [20], [24], [27]):

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 20^{th} doubling of primary BC (Fig. 2). It allows us to define the nonvisible growth period of MTS and the initial period of nonvisible MTS manifestation;
4) the *whole nature history* of the PT and secondary distant MTS is 60 doublings (Fig. 3).

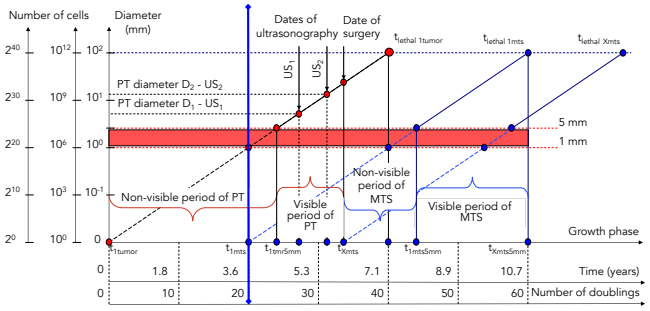

Fig. 2. The first MTS cell appears on the 20^{th} doubling of PT

The CoMPaS is based on exponential growth model and consisted of nonlinear and linear determined equations [3]–[14], [18], [20]–[22], [24], [27]:

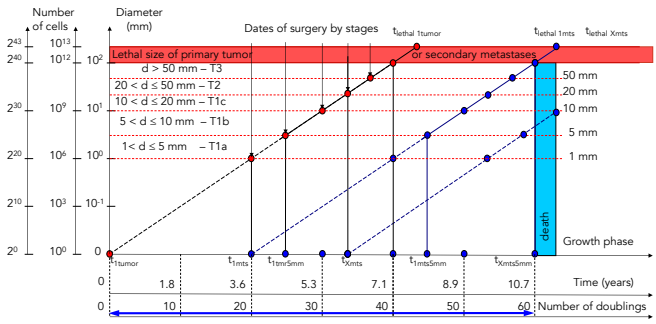

Fig. 3. The *whole nature history* of the PT and secondary distant MTS is 60 doublings

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

$\frac{\log 2}{DT}$	—	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 **nonvisible** 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 the PT and secondary distant MTS.

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) ($\Delta t = t_1 - t_0$) [24]:

$$DT = \frac{\log 2\ (\Delta t)}{\log V_1 - \log V_0}$$

*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.) [1], [28]. Five-year survival rate of stage IV is about 20-25% among BC patients [16]. Unfortunately, the available papers for this 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.

The CoM-IV rests on CoMPaS and complemented by formulas that describes correcting coefficient 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:

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

$pMts_{\log(m)}$ — 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 the PT ($TVDT_{pT}$);
$pMts_{\log(V)}$ — the number of primary MTS doublings.

III. Results

Whole Natural History and calculations

The *"whole natural history"* of PT and **primary** MTS growth of BC for different stages (parameter T from TNM), according to CoMPaS and CoM-IV. Tab II provides calculations for the *whole natural history* of stageIV.

Legend of Tab. II:

- TNM parameters depend on PT size: T1, T2, T3, T4, N1, N2, N3, M1 [1] (see detailed description on Tab. I);
- row 1 uses data from tables of paper [28];
- row 2 is calculated from row 1;
- row 3 uses data from figure of paper [16];
- $pT_{(D)}$ means a mean size (mm) of primary tumor at surgery (removal PT);
- $pT_{\log(V)}$ means the number of doublings of PT at surgery (removal PT);
- $TVDT_{pT}$ means a mean tumor volume doubling time of PT at surgery (removal PT);
- $pMts_{(D)}$ means a mean size (mm) of primary distant MTS at surgery (removal PT);
- $KpMts$ means a mean correcting coefficient of MTS growth rate.

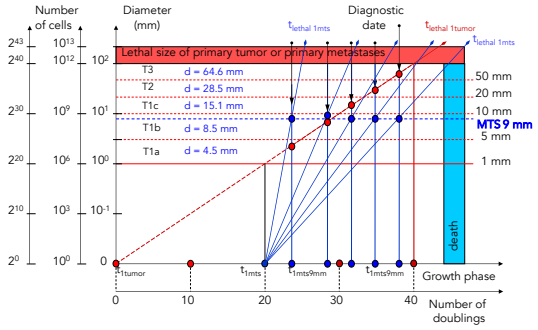

Fig. 4. Scheme of the whole natural history of BC. **Stage IV**

TABLE II

	pT1aN1-3M1 (Fig. 5)		
$pT_{(D)}$	**5.0**	**4.5**	**5.0**
$pT_{log(V)}$	26.9	26.4	26.9
$TVDT_{pT}$	**80.0**	**80.0**	**80.0**
$pMts_{(D)}$	5.0	9.0	50.0
$pMts_{log(m)}$	26.9	29.4	36.9
K_{pMts}	3.9	4.6	5.34
$TVDT_{pMts}$	20.5	17.4	15.0
	pT1bN1-3M1 (Fig. 6)		
$pT_{(D)}$	**5.0**	**8.5**	**10.0**
$pT_{\log(V)}$	26.9	29.2	29.0
$TVDT_{pT}$	**75.0**	**75.0**	**75.0**
$pMts_{(D)}$	5.0	9.0	50.0
$pMts_{\log(m)}$	26.9	24.9	36.9
K_{pMts}	3.9	3.2	3.72
$TVDT_{pMts}$	19.2	23.4	20.1
	pT1cN1-3M1 (Fig. 7)		
$pT_{(D)}$	**10.0**	**15.1**	**20.0**
$pT_{\log(V)}$	29.9	31.7	32.9
$TVDT_{pT}$	**70.0**	**70.0**	**70.0**
$pMts_{(D)}$	5.0	9.0	50.0
$pMts_{\log(m)}$	26.9	29.4	36.9
K_{pMts}	2.7 2	2.52	2.86
$TVDT_{pMts}$	25.8	27.8	24.5
	pT2N1-3M1 (Fig. 8)		
$pT_{(D)}$	**20.0**	**28.5**	**50.0**
$pT_{\log(V)})$	32.9	34.4	36.9
$TVDT_{pT})$	**65.0**	**65.0**	**65.0**
$pMts_{(D)}$	5.0	9.0	50.0
$pMts_{\log(m)}$	26.9	29.4	36.9
K_{pMts}	2.09	2.04	2.19
$TVDT_{pMts}$	31.2	31.8	29.7
	pT3N1-3M1 (Fig. 9)		
$pT_{(D)}$	**50.0**	**64.6**	**70.0**
$PT_{\log(V)})$	36.9	38.0	38.3
$TVDT_{PT})$	**60.0**	**60.0**	**60.0**
$pMts_{(D)}$	5.0	9.0	50.0
$PMts_{\log(m)}$	26.9	29.4	36.9
K_{PMts}	1.59	1.64	2.01
$TVDT_{PMts}$	37.7	36.7	29.8

A. Limitations

Model describes **only** stage IV of breast cancer [2], [3], [14].

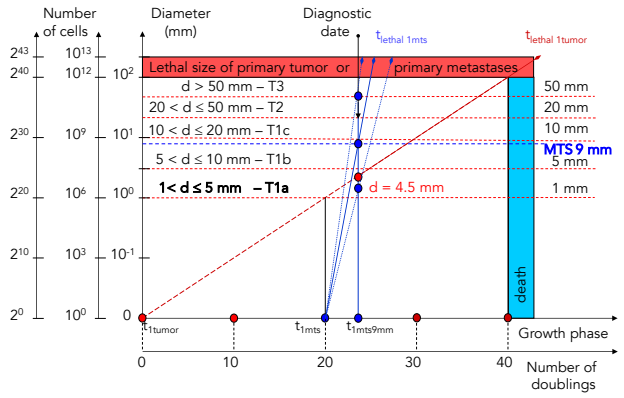

Fig. 5. **pT1aN1-3M1**

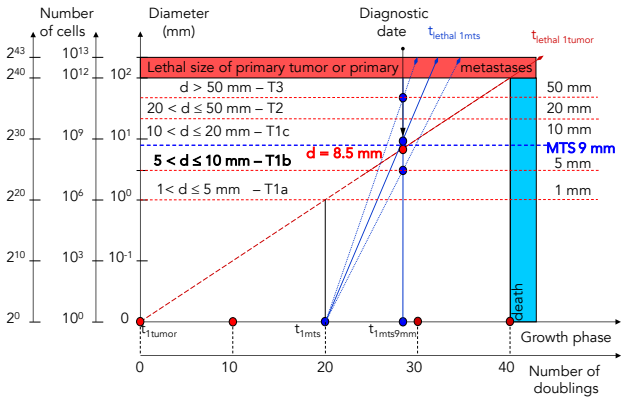

Fig. 6. **pT1bN1-3M1**

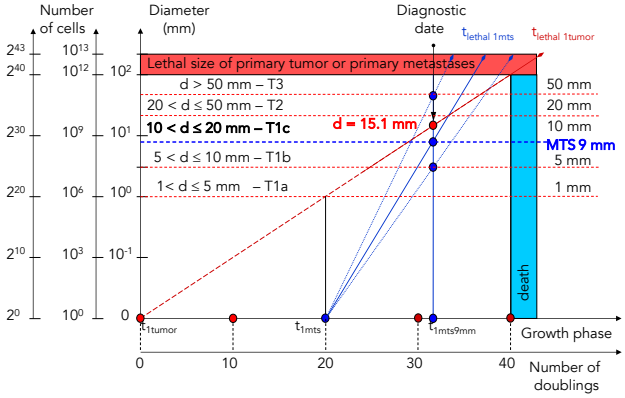

Fig. 7. **pT1cN1-3M1**

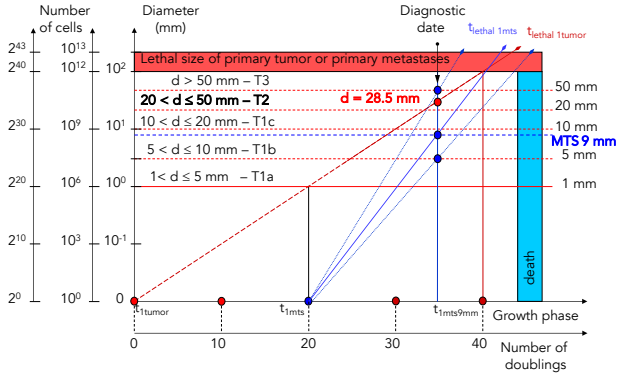

Fig. 8. **pT2N1-3M1**

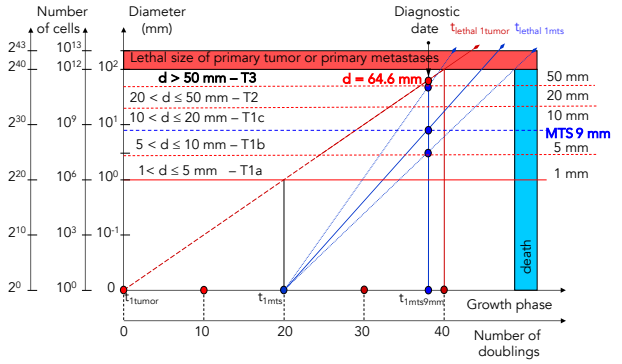

Fig. 9. **pT3N1-3M1**

B. Summary

The *"whole natural history"* of PT and **primary** MTS growth of BC for different diameters of primary tumor (parameter T from TNM) was described via CoM-IV.

The CoM-IV allows us to calculate different growth periods of PT and primary MTS: 1) "non-visible period" for primary tumor; 2) "non-visible period" for primary MTS; 3) "visible period" for primary MTS.

Tab. III illustrates the variety of K_{pMts}. The higher K_{pMts} is, the shorter $TVDT_{pMts}$, the lower lifetime of patient and the worse forecast are.

TABLE III
SUMMARY

Stage	**Primary MTS**	K_{pMts}
pT1a (1 mm < d ≤ 5 mm)	5 mm < d ≤ 50 mm	3.90 - 5.34
pT1b (5 mm < d ≤ 10 mm)		3.72 - 3.90
pT1c (10 mm < d ≤ 20 mm)		2.72 - 2.86
pT2 (20 mm <d ≤ 50 mm)		2.09 - 2.28
pT3-4 (50 mm <d)		1.59 - 2.01

Predictor

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

TABLE IV
INFORMATION

Developer	Ella Tyuryumina
Category	Medicine
Updated	5.04.2017
Version	2.0
Size	29 MB
Compatibility	Requires iOS 9.1 or later. Compatible with iPhone and iPod touch
Languages	English

INPUT DATA:

- the first ultrasound diagnostic data:
  - date (dd.mm.yyyy)
  - diameter (mm)
- the second ultrasound diagnostic data:
  - date (dd.mm.yyyy)
  - diameter (mm)
  - diameter of primary MTS (mm)

OUTPUT DATA:

- forecast:
  - the number of months
  - category of forecast:
    - favorable
    - mid-favorable
    - unfavorable

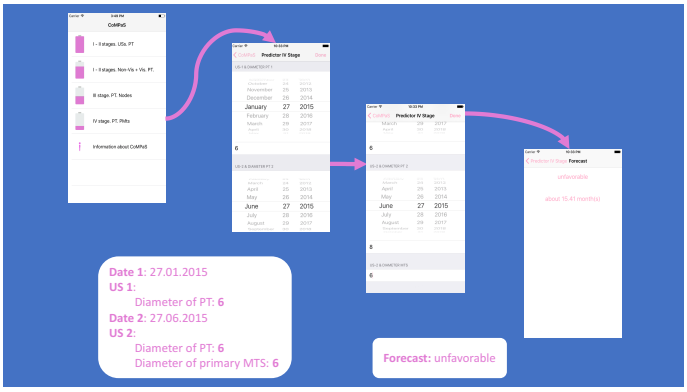

Fig. 10. Clinical example CoM-IV

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 us 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 which makes forecast using only current patient data, whilst the others are based on the additional statistical data.

IV. Conclusion

The CoM-IV: a) describes correctly PT and primary distant MTS growth of IV (T1-4N0-3M1) stage with (N1-3) or without regional MTS in lymph nodes (N0); b) facilitates the understanding of the survival period of patients with primary MTS (T1-4N1-3M1 stage IV).

The CoM-IV describes correctly (T1-4N1-3M1 stage IV): 1) the period of PT growth and corresponds to TNM classification (parameter T); 2) the period of primary distant MTS growth and 5-10 years survival of patients with stage IV of BC.

The CoM-IV calculates the variety of correcting coefficients of primary MTS growth rate, relating with PT growth rate. The constraints of application CoM-IV are imposed.

At this stage, it is relevant to dwell upon the work still to be done: 1) testing the CoM-IV on clinical data; 2) analysing forecasts statistically; 3) expanding the limits of applicability of the CoM-IV, in other words, add parameters that correspond to affected lymph nodes (N1-3); 4) implementing CoM-IV to medical practice.

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