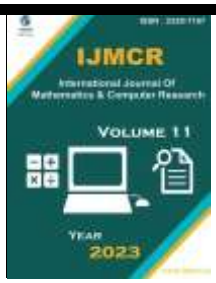
International Journal of Mathematics and Computer Research

ISSN: 2320-7167

Volume 11 Issue 01 January 2023, Page no. – 3156-3177

Index Copernicus ICV: 57.55, Impact Factor: 7.362

DOI: 10.47191/ijmcr/v11i1.08



Radiotherapy Genetic Algorithm Pareto-Multiobjective Optimization of Biological Efective Dose and Clonogens Models for Head and Neck Tumor Advanced Treatment

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ARTICLE INFO

Published Online:
20 January 2023

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ABSTRACT

BED model (Biological Effective Dose) for Head and Neck tumors Hyperfractionation TPO was optimizedwith Pareto-Multiobjective (PMO) Genetic Algorithms (GA) software. Artificial Intelligence (AI) with GA is applied on Radiotherapy Treatment Planning Optimization (TPO). Secondly, the review of $N_{Effective}$ (Effective Tumor Population Clonogens Number) model optimization for breast cancer clonogens parameters determination in TPO (Treatment Planning Optimization) is got with 3D Graphical and Interior Optimization methods. Results series comprise PMO imaging process sequences and numerical values of PMO and $N_{Effective}$ model for Head and Neck cancer parameters. Further results demonstrate PMO-GA BED model both with Pareto-Optimal Front detailed graphics, charts and numerical dose fractionation datasets. Supplemental review of new recent applications with 3D Isodoses TPO with AAA (Anisotropic Analytic Algorithm) model wedge filters dose delivery is shown. Advanced RT Head and Neck cancer TPO, and tumors in general for Fractionation-dose protocols are explained.

KEYWORDS: Pareto-Multiobjective Optimization (PMO), Mathematical Methods (MM), Biological Models (BM), Radiation Therapy (RT), Initial Tumor Clonogenes Number Population (N_0), Effective Tumor Population Clonogenes Number (N_{Eff}), Linear Quadratic Model (LQM), Integral Equation (IE), Tumor Control Probability (TCP), Biological Effective model (BED), Tumor Control Cumulative Probability (TCCP) ,Radiation Photon-Dose (RPD), Nonlinear Optimization, Radiotherapy Treatment Planning Optimization (TPO), Source-Surface Distance (SSD), Software Engineering Methods, Radiation Photon-Dose, Attenuation Exponential Factor (AEF), Nonlinear Optimization, Radiotherapy Wedge Filter (WF), Anisotropic Analytic Model (AAA), Fluence Factor (FF), Omega Factor (OF), Treatment Planning Optimization (TPO), Breast Tumor (BT), Artificial Intelligence (AI), Pareto-Multiobjective (PMO), Genetic Algorithms (GA) .

INTRODUCTION

The objective of this research is to apply Artificial Intelligence in Evolutionary Algorithms with Pareto-Multiobjective Optimization on two radiotherapy BMs. Additionally, computational software to present new 3D Isodoses graphs with WF dose delivery in AAA model is shown. The BMs studied are for Head and Neck modern radiotherapy TPO, Table 1 [enhanced in Appendix].

Evolutionary Algorithms are similar, but different than Monte Carlo stochastic methods. The difference is that Monte Carlo method is based on continuous random variation of parameters to get the objective function optimized. Instead, Evolutionary algorithms select the optimal parameters by means of interchanging the best generations parameters among those generations that show best optimality results. Evolutionary Algorithms constitute a fundamental base for Artificial Intelligence fundamentals in radiotherapy TPO. BMs provide with better experimentally-based accuracy for RT optimal treatment, in order to avoid excess of radiation on OARs and get the best NTCP [1-21,74-85].

For these purposes Nonlinear GA-PMO engineering software was designed in a number of programs for PMO-BED models. The second model for $N_{Effective}$ (Effective Tumor Population Clonogens Number) is optimized with 3D

Graphical optimization programs and imaging processing techniques constitute an improvement from previous contributions [75,85].

Table 1.-Brief of RT TPO methods and subsequent positive effects in patient cure and post-radiation life. Those are justified also for the rise of head and neck tumor survival time and complete cure got by modern RT, IMRT, IMPT, Chemo, and Inmunotherapy advances. Enhanced in Appendix.

Therefore, innovation of this article is to present and prove the GA utility to obtain optimal results for two BMs. First one, BED model for breast cancer RT treatment. Its Hyperfractionation doses, treatment time with delays tolerance intervals, and optimal number of fractions were determined. The second model [75,85], corresponds to $N_{Effective}$ (Effective Tumor Population Clonogens Number) model, [Fowler, J, 1989- 2010,83] . It is a review and improvement/innovation from [20,21,75,85]. 3D Graphical Optimization for $N_{Effective}$ rate with a range of N_0 clonogens magnitude was shown in improved results from [20,21,75,85].

GA findings are presented both in 2D graphics and dataset. Numerical results and applications to improve head and neck tumor RT treatment are detailed in Tables 4-6. Additionally,

$N_{Effective}$ MODEL FOR HEAD AND NECK TUMORS APPLICATIONS	
RT TPO METHOD IMPROVEMENTS	**DIRECT EFFECT**
Mathematical Improvements when N_{Eff} is implemented in Survival Fraction Models	With N_{Eff} Implementation TCP is numerically more accurate Without N_{Eff} TCP is falsely numerically higher With N_{Eff} Implementation NTCP is numerically more accurate Without N_{Eff} Implementation NTCP is falsely numerically lower
N_{Eff} Implementation in Survival Fraction Models	Dose Delivery Precision because it minimizes Clonogenes growth during radiotherapy Treatment Time, Maximum Effect/Maximum Tumor Control Probability [TCP]
N_{Eff} Implementation in Survival Fraction Models for exact calculation of NTCP instead N_0 . Then, TCP and NTCP are more efficacious.	Radioprotection OARs Dose Precision because it sets exact Clonogenes growth during radiotherapy Treatment Time, Maximum Effect/Maximum Normal Tissue Complications Probability [NTCP]
Optimization of Biological Models	Dose Delivery Precision, minimum dose/ maximum effect
Previous Photon-dose Optimization	Dose Delivery Precision to be implemented in BM, minimum dose/ maximum effect
Normal Tissue Complications Probability Models [NTCP]	Dose-Volume-Histogram Dose Delivery Precision to be implemented in BM, minimum dose at OARs
ON PATIENT EFFECTS	
OARs Radioprotection	Avoid Damage at any FSUs [Organ Funcional Subunits]
Radiation Therapy Secondary Effects	Hypo Fractionations decreases Radiation Undesirable Symptoms
Patient Life Quality	Not only Physical benefit but also Psychological for Patient

new 3D Isodose graphics for TPO with AAA model in WF beam-modification delivery, at isocenter depths [z = 5,15 cm], is proven and graphically detailed. 3D Isodoses types are defined and shown, from Type I ,Vertical, Type II, Horizontal, and Type III, mixed-up, vertical and horizontal.

Succintly, Nonlinear Pareto-Multiobjective GA optimization was performed for BED and $N_{Effective}$ models in breast cancer TPO. Further, 3D Graphical Optimization and 3D Isodoses are shown and demonstrated.

Several studies were developed in radiotherapy TPO with biological models and algorithms simulations [19,74]. The objective of this contribution is to present 3D Graphical Optimization simulations for $N_{Effective}$ clonogens population with Fowler model [82,84]. It was set initially without implementation in Linear Quadratic Biomodel equations for BED dose delivery. Specifically for head and neck cancer with its corresponding specific parameters [22,82,83,84].

Radiotherapy combined with Radiation Protection for the patient during routinary RT treatment with BMs avoids multiple risk factors. Namely, RT overdose, OARs damage, increase of radiation use for high incidence/prevalence of any type of cancer with subsequent RT oncology therapy, medical staff professional cumulative dose increase, hospital radiation contamination, environmental radiation contamination, and others [1-20,22-25, 73-79,82,83]. Table 1 shows the direct effect of BMs in TPO and the precision improvements given by $N_{Effective}$ clonogens model application in Linear Quadratic models and BED ones. For head and neck cancer RT TPO, the hyperfraccionated radiotherapy protocol us usually 45-60 Gy during 6-8 weeks, with about 5 fractions/weekly. However, these magnitudes/schedules vary according to hospital or Oncology center criteria.

Head and neck tumors group present a number of proper oncological, epidemiological, pathogenesis, and radiobiological characteristics [75-79, 83]. Namely, the external media intake/contact from a group of substances that have significant pathogenesis factors in the oncological origin of these cancers. These intakes could be toxic substances or biological ones, such as virus or bacteria. Among virus, for example, the Espstein-Barr one is linked to Nasopharyngeal carcinoma pathogenesis, and Papillomavirus to Tonsillar carcinomas. That is, the head, thorax cavity and neck anatomical zones catch from air many of them from exterior media into the mouth nose, and lungs. Therefore tobacco influence is epidemiologically-statistically high. The oral cavity accumulates tobacco and alcohol as oncogenetical factors. The lungs could also take in materials that cause mesothelioma. Specific processed substances contained in food could cause oncogenesis phenomena in oral cavity, esophagus and stomach. External radiation sources show an important influence for thyroid cancer origin [83,84]. Electromagnetic radiation constant and daily magnitude may have epidemiological influence in specific brain cancer tumors pathogenesis.

Therefore, following the Radiation Therapy research studies series, [1-20,73-79,84,85], this study objective is the implementation of GA-TPO for optimal head and neck tumors radiotherapy. Second one is to obtain results for Tumor Clonogens Effective Population Number Model for head and neck cancer, [82]. Photon-dose AAA model former contributions results in breast tumors Biological Models (BM) TCP parameters, [19,74]. Development for 3D Graphical Optimization solutions from recent study [19,74] to furher obtain the Effective Tumor Clonogenes Survival Rate [$N_{Effective}$], constitutes the aim of this research. Photon-beam Biological Models are based mainly on exponential

functions with radiobiological parameters, namely [α , β], whose magnitudes are determined in general with ***in vitro*** experimental [19,21-24,74]. These parameters are implemented in BM to obtain Survival Fraction Clonogens Rate, [N_S] , [19,21-24,74,82]. N_S is function of [N_0], namely, initial clonogens population number.

The innovation of this study determines the modern applications of Artificial Intelligence Evolutionary methods on BED model. Additionally, the fitted clonogens population model for RT treatment is optimized. Initial clonogens population number results with the calculation of $N_{Effective}$ for head and neck tumors RT treatment [19,22,74,83,84] are proven. Table 6 shows applications of [$N_{Effective}$] calculations for RT head and neck cancer. The new 3D Isodoses TPO charts are shown and reviewed/improved from [84] with specific programming to prove the applications of this precision-step in BED and Linear Quadratic models.

Research 3D imaging and numerical results comprise simulations for $N_{Effective}$ clonogens population model related to RT treatment delay time parameters and population doubling time head and neck tumors constants [19,74,83].

Succintly, Nonlinear Pareto-Multiobjective GA optimization was performed for BED and $N_{Effective}$ models in breast cancer TPO. Further, 3D Graphical Optimization and 3D Isodoses are shown and demonstrated. In summary, additional 3D Graphical Optimization was programmed specifically for $N_{Effective}$ clonogens population model. Results comprise 3D image processing charts and numerical approximations useful in TPO in radiotherapy, Figures 1-4, Table 4. 3D Isodoses image-processing AAA model with WF developments from [84] are shown and proven, Figures 5-6.

MATHEMATICAL METHODS AND SOFTWARE

Two models have been optimized. The first one, Equation 1, is the most innovative, based on artificial intelligence basics of Evolutionary Algorithms. $BED_{Effective}$ model implemented is the primary one, because refinements/variations were presented in literature later on [24].

The second model constitutes an improvement for [20,75,85] publications. Its software and imaging processing perspectives were enriched, Equation 2.

The programming method(s) applied for this research are based in a number of previous papers [1-20,74]. For $N_{Effective}$ in Equation 1 implementation 3D programs adjustments were required. Table 2, enhanced in Appendix, shows for second clonogens model the 3D programming method variations to obtain acceptable better calculations, and 3D Graphical Optimization processing images, error determinations, and get applied exactly the $N_{Effective}$ model, [Equation 1 formulation].

Formulation for Pareto-Multiobjective GA BED Model

Designed for Pareto-Multiobjective Optimization, the basic $BED_{Effective}$ model was implemented, [24]. This BED model constitutes the fundamentals for fractionate radiotherapy. Therefore, the following algorithm was set [Sketch 1],

Chebyshev L_1 Optimization for,

$$BED_{Effective} = k\,d\left[1+\frac{d\times\beta}{\alpha}\right]-\ldots$$

$$\ldots-\frac{Ln(2)}{\alpha}\left[\frac{T_{Treatment}-T_{Delay}}{T_{Potential}}\right];$$

(1)

where

k : Dose fraction number for hyperfractionated RT protocol. [20-25] .
Software pattern set [35 , 45] Fractions.
d : Dose fraction for hyperfractionated RT protocol. [20-25] .
Software pattern set [1 , 2.2] Gy.
α : Clonogen Head and Neck tumor radiosensitivity parameter [0.19 , 0.61]. [20-25] .
β : Clonogen Head and Neck tumor radiosensitivity parameter [0.0581] . [20-25] .
$T_{Treatment}$: Total time for radiation dose delivered.
Software pattern set [22 , 55] days. [20-25] .
T_{Delay} : Total standard repopulation delays for RT.
Software set [21] days. [20-25] .
$T_{Potential}$: Total standard Head and Neck cancer potential repopulation factor.
Software pattern set [3.5 , 4.5] days. [20-25] .

Sketch 1.- Head and Neck PMO algorithm [Casesnoves, 2021-2022] implemented in software. The intervals for optimization parameters in software are detailed.

Formulation for $N_{Effcetive}$ Clonogens Model

For determination of $N_{Effective}$ Clonogens population number, [75,85], a standard model was selected for [Fowler, J, 1989-2010]. The experimental parameters for head and neck cancer RT treatment TPO protocol are shown in Table 1, based on [20-25,75,85]. This mathematical model for Effective Number of Clonogens population during RT treatment time, whose equation was detailed from [23,24] reads,

$$N_{Effective} = N_0 \times 2^{\left[\frac{(T - T_{Del})}{T_{Pot}}\right]};$$

(2)

where

$N_{Effective}$: Number of tumor clonogens in function of RT treatment protocol time.

N_0 : Initial Clonogens Number at starting RT time.

T : Total RT Treatment time.

T_{Delay} : Number of delay days after standard RT treatment time.

$T_{Potential}$: Potential Tumor Doubling Clonogens time.

$N_{Effective}$ parameter is important for TPO with BMs. The implementation of these parameters, Table 2 into BMs provides with accuracy in TCP, BED, and NTCP essential determinations for TPO. Biomodels equations depending on N_0 and $N_{Effective}$ are not very complicated, and based usually on exponential functions, statistical distributions [Binomial or Poisson] usually, and two radiosensitivity key parameters. Namely, [α and β biological modelling parameters], whose magnitudes intervals can be determined by ***in vitro*** or ***in vivo*** experimental. An Integral Equation Model (IEM) for TCCP, based on new Linear Quadratic Model and Statistical Binomial Distribution approximation was published in recent contributions [20,75,85]. The simplest Linear Quadratic model modified equation was published [75,85].

Dataset and approximations for head and neck cancer implemented into Eq.2 model is shown in Table 2, [20-25,75,85] .

Previous Formulation for Linear Quadratic $N_{Survival}$ Clonogens Model

Here the application of this $N_{Effective}$ model simulations on further Biomodels equations depending on N_0 and $N_{Effective}$ are explained. That set can be done into Linear Quadratic model, which is based usually on exponential functions, statistical distributions [Binomial or Poisson, 21-24,74] , and two radiosensitivity key parameters, namely [α and β biological modelling parameters] . An Integral Equation Model (IEM), based on new Linear Quadratic Model and Statistical Binomial Distribution approximation was published in recent contributions [19,74]. The simplest Linear Quadratic model equation set in [19,74] reads,

Elementary Biological Model for clonogenes survival population N_S ;

$$N_S = N_0 \times e^{-[\alpha D + \beta D^2]};$$

(3)

where

Ns : Initial number of tumor clonogens

No : Surviving number of tumor clonogens

α : Clonogen radiosensitivity parameter

β : Clonogen radiosensitivity parameter

D : Total radiation dose delivered

Parameters [α and β] are interrelated each other [β/α] and to N_0 magnitude. Parameter [α] is related to N_0 magnitude [22], although an average value is generally implemented. Both [α and β] measurements are taken ***in vitro*** [19, 21-25,74]. Equation (3) is more complicated in practice for a number of constraints. Firstly, the dose D is hyperfractionated/hypofractionated in the TPO clinical practice [19,21-25,74]. Secondly, a function-factor K [21], has to be introduced for implementation in further exponential BM, although that factor is discussed. However, fractional dose factors, d, and number of fractions n, [21], are omitted in (3) for simplification, and are not relevant for the mathematical method development. In the standard BM research, [19,21-25,74], the quotient [σ/β] is generally considered constant. In this study, however, alpha and betha radiosensitive parameters are set independently. The reason is avoid too many approximations. By using 100% percentages and 1% rates for $N_{0,Survival}$, the model can be better implemented in Statistical Distributions to obtain TCP formulation, with Poisson, Binomial, and Normal-Gaussian distributions. Through this modification, [Casesnoves, 2022], several numerical inconvenients are sorted. This variant, using percentages and rates of N_0 implies to make calculations setting parameters [α, mainly, and β] values in function of N_0 , for example [66, Table 44.2]. Figure 1 in [74] shows an original logarithmic fitness numerical equation from these values [from 22 experimental data]. Thus, the modified BM equation reads,

Percentage and rate [% or 1%],

$$N_S\,[\%] = N_0\,[100\%] \times e^{-[\alpha D + \beta K D^2]};$$

or in rate,

$$N_S\,[1\%] = N_0\,[1\% = 1] \times e^{-[\alpha D + \beta K D^2]};$$

[Casesnoves 2022];

(4)

where

Ns : Initial number of tumor clonogens
No : Surviving number of tumor clonogens
α : Clonogen radiosensitivity parameter
β : Clonogen radiosensitivity parameter
D : Total radiation dose delivered
K : Lea-Catcheside function-factor K, [21]

This approximation, [19,74] Equations (3-4), facilitates further calculations and improved models. However, setting percentages and/or rates for N_0 is conditioned for the magnitude changes of [α, β] related N_0 [22, Table 44.2, and 2D Logarithmic Figure 1 at 74] .

HEAD AND NECK TUMORS CLONOGEN REPOPULATION DURING TREATMENT RT TIME MODEL DATASET FOR SIMULATIONS		
PARAMETER	**COMPUTATION INTERVAL**	**DETAILS**
HEAD AND NECK TUMOR N_0	[10^3 , 10^{11}] clonogens	This interval was selected from [22,80,81,83]
T Standard RT Time	Fixed days [22,46]	This interval was selected from [22,80]. However it varies according to authors [25], depending on Conventional, Hiper or Hypo Fraccionated RT treatment time
T_{Delay}	Fixed days, when clonogens start mitosis	It was supposed weekends or hospital break days and unpredictable delays [80,81,83]
HEAD AND NECK TUMOR $T_{Potential}$	$T_{Potential}$ ∈ [5,6] days ; [80,81,83]	Head and Neck cancer in vivo data selected from [80,81,83]

Table 2.- The simulations were done with approximate numerical-experimental data from several authors. $T_{Potential}$ in breast cancer is taken 14 days. However, that figure is an approximation based on radiobiological experimental. Simulation dataset from [19,21-25,74,75,80,81,85] . Enhanced in Appendix.

$N_{Effective}$ MODEL MATLAB SOFTWARE METHOD(S)		
COMPUTATIONAL OBJECTIVE	**PROGRAMMING DEVELOPMENT**	**COMMENTS**
Implementation of experimental parameters for T_{Delay} , $T_{Potential}$,N_0	Precision required to get true simulations for head and neck tumors	Those parameters differ for every type of tumor
Optimization of implementation of $N_{Effective}$ for fast running time and imaging quality	Precision required to organize and optimize correct order, loops, patterns, and exactitude of every imaging processing subroutine	It is necessary to select the most appropriate subroutine, among several imaging processing sources for getting good 3D charts
Imaging processing refinement	Logarithmic scale changes were necessary because of the high numerical magnitude of some parameters	Several imaging processing solutions can be used.
Imaging processing matrices size optimization for final 3D plots	To get good-quality 3D model images it is necessary optimize, select, and order the best imaging-tiles matrices size combination linked to imaging processing tools	Not always bigger tiles number implies better imaging quality

Table 3.- $N_{Effective}$ model main parameters for 3D Graphical simulations [1-20, 74] . Program software parts numerically calculated for Equations 1-3. The data/method from Tables 2-3 was implemented.

RESULTS

Figures 1-5 show PMO results. Table 4 details numerical PMO results. The most important to check the validity of results is Figures 1-2 that shows Pareto Front of the objective function of Equation 1. Average distance among generation individuals is presented in Figure 3. Number of generations selected was 300-800. Score histograms prove the validity of the software and PMO done.

Results for Pareto-Multiobjective BED Model

Imaging processing PMO results are presented in imaging processed chart commented, Figures 1-5. Brief of Numerical Results from software are included in Table 4.

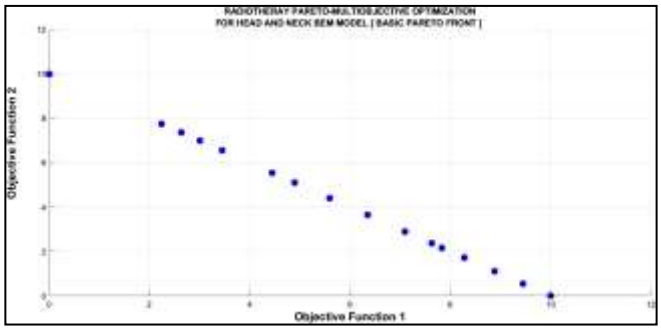

Figure 1.-This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f_1 and f_2 show low residuals. Therefore, results are acceptable. The number of points on the Pareto front was: 18. The number of generations was : 300. Enhanced in Appendix.

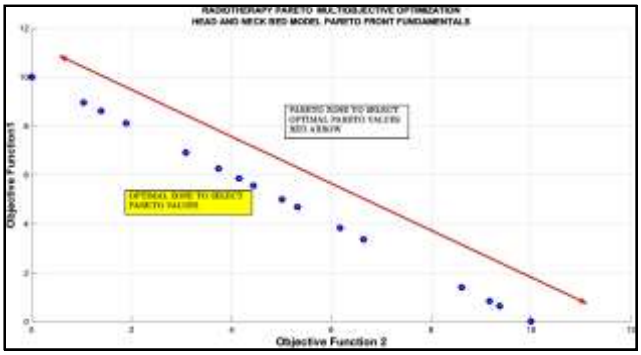

Figure 2.- This is the lined-marked inset graph showing the Pareto Front. Since the number of functions calculated is quite high, the points that show the distance vary significantly for 300 generations. The fundamentals of PMO calculations are usually based on 2D PMO functions charts. In this study both Objective f_1 and f_2 that show low residuals. Enhanced in Appendix.

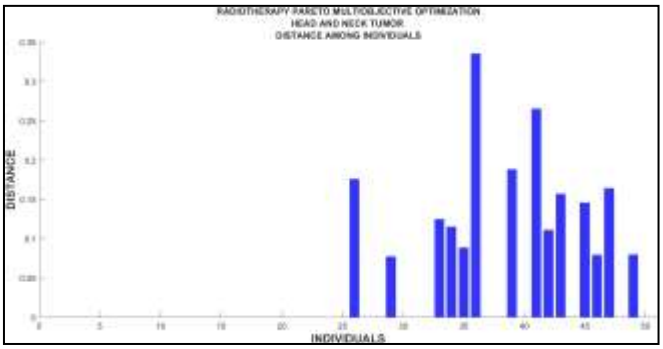

Figure 3.-Complementary 2D graphs showing distance among individuals. Results are acceptable.

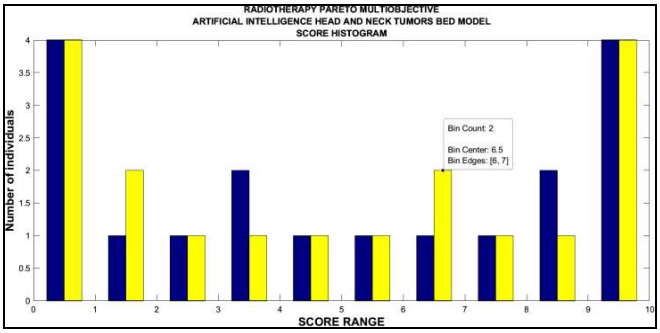

Figure 4.-Complementary 2D graphs showing that 100% criteria is met and number of individuals paired-histograms versus score range. Objective f_1 and f_2 are differentiated by blue and yellow colors. Enhanced in Appendix

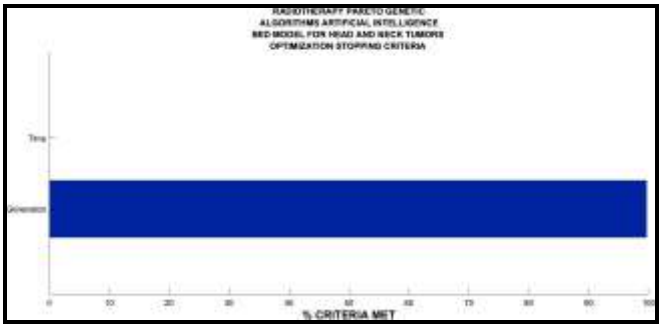

Figure 5.-Complementary 2D graphs details showing stopping criteria with acceptable results.

Brief of PMO Head and Neck Numerical Results

Numerical results resume for PMO in BED model are detailed in Table 4. Chebyshev norms were set for [55 , 65] Gy interval. Dose fraction magnitude should be less than 2 Gy approximately. Numerical Results for $N_{Effective}$ model are developed and reviewed from the innovation from [20,21,75,85].

BRIEF OF NUMERICAL RESULTS FOR PMO OPTIMIZATION WITH GA FOR HEAD AND NECK TUMOR BED MODEL	
PARAMETER	INTERVAL OPTIMIZATION RESULT
OPTIMAL HYPERFRACTIONATION DOSE Gy	[1.163 , 1.3415] Gy
OPTIMAL TIME TREATMENT AFTER STANDARD 21 DAYS	[18 , 20] Days (after 21 standard days)
OPTIMAL DOSE FRACTIONS NUMBER	[38 , 50]
The number of points on the Pareto front was: 18 The number of generations was : 300	

Table 4.-Brief of PMO Artificial Intelligence with GA optimization numerical results in Head and Neck tumors for advanced TPO. Enhanced in Appendix.

Review and Results for $N_{Effcetive}$ Clonogens Model

Figures 6-9 show 3D results for $N_{Effective}$ magnitudes in function of N_0 and RT head and neck cancer treatment extension time. Remark that implementation of $N_{Effective}$ 3D model and corrections for BED and Linear Quadratic optimal dose delivery magnitudes will be developed in upcoming contributions [84]. Figures, 6-7 are set with axes-selected logarithmic scales. Figures 8-9 are intended to show the $N_{Effective}$ magnitude to be set in biological Linear Quadratic models [74]. Figure 9 was imaging-processed in grayscale and box format to prove a sharp calculations perspective. Table 5 presents some maxima/minima numerical data for clonogens second model.

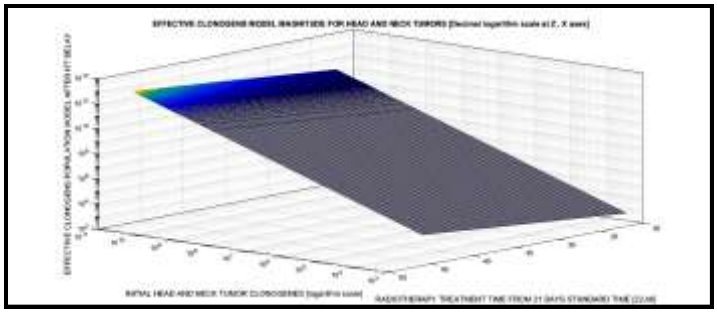

Figure 6 .- $N_{Effective}$ Rate simulation 3D image for head and neck tumors. At Z axis, logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. Matrices for Image Processing have about [100-250 x 100-250] elements. At figure, inset, axes interval modifications explained.

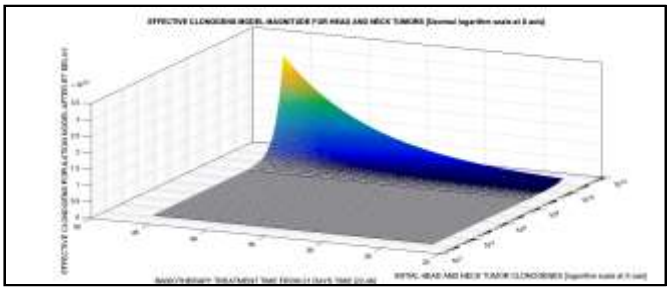

Figure 7 .- $N_{Effective}$ Rate simulation 3D image for head and neck tumors. At X axis, logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The image processing perpective was set to

demonstrate the almost exponential/parabolic increase of $N_{Effective}$ magnitude from clonogenes population approximate value 10^8 . The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [100-250 x 100-250] elements. At figure, inset, axes interval modifications explained. Enhanced in Appendix.

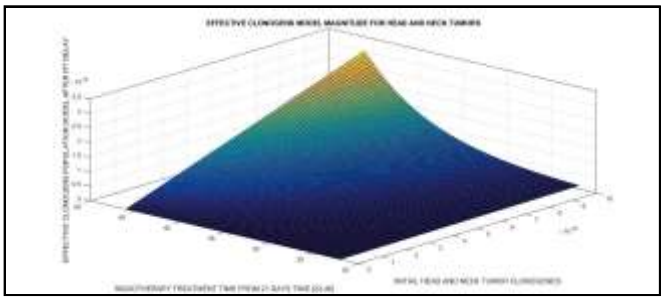

Figure 8 .- Matlab $N_{Effective}$ Rate simulation 3D image for head and neck tumors. Image was set without any logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [100-250 x 100-250] elements. At figure, inset, axes interval modifications explained.

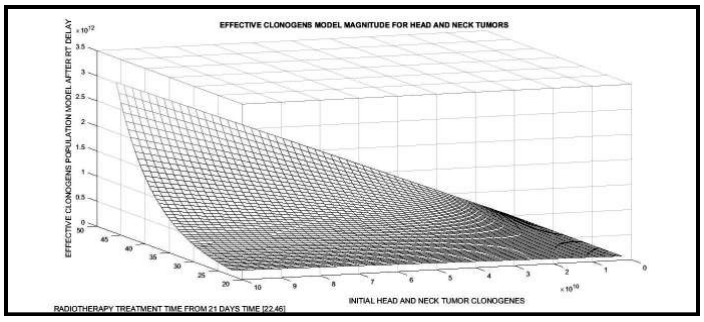

Figure 9 .- Grayscale-processed with magnitude boxes Matlab $N_{Effective}$ Rate simulation. 3D image for head and neck tumors shown. Image was set without any logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The grayscale image processing perpective was set to demonstrate the almost exponential/parabolic increase of $N_{Effective}$ magnitude from clonogenes population approximate value 10^8 . The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [100-250 x 100-250] elements. At figure, inset, axes interval modifications explained. Enhanced in Appendix.

NUMERICAL RESULTS FOR $N_{Effective}$ MODEL IN HEAD AND NECK TUMORS

Minimum [N_0] Minimum [T_{Delay}]	Minimum [$N_{Effective}$] Minimum [T_{Delay}]	Maximum [N_0] Minimum [T_{Delay}]	Minimum [$N_{Effective}$] Maximum [T_{Delay}]	Maximum [N_0] Maximum [T_{Delay}]	Maximum [$N_{Effective}$] Maximum [T_{Delay}]
1000 1.49 days	1117 1.49 days	1.00×10^{11} 1.00 days	3.01×10^{4} 27-28 days	1.00×10^{11} 27-28 days	3.01×10^{12} 27-28 days

Table 5.- Some Maxima and Minima of Numerical results for second model parameters. 3D image processing data. Enhanced in Appendix.

REVIEW OF 3D ISODOSES APPLICATIONS

At Figures 10-11, a review of primary demonstration of new 3D Isodoses Treatment Planning System, [Casesnoves invention, 2022], were explained and published previously [85]. There are three 3D Isodoses types. Namely, Type 1 [Vertical 3D Isodoses, Figure 10], Type 2 [Horizontal 3D Isodoses, Figure 11], and Type 3 [Combination of Vertical and Horizontal 3D Isodoses, according to requirements of the planning systems, and the geometry of the tumor for imaging guided RT] in contrast to classical 2D Isodoses. 3D Isodoses radiotherapy simulations software was presented through a 3D graphics series engineering software [85]. Figures 10-11 show improved 3D Isodoses image processing for 18 Mev with [z= 5,15 cm] AAA model dose-deposition isocenter depths [1-20,83-85]. These depths are convenient for example, in TPO for mammary glands RT treatment [that is, size ranges, from small glands to bigger ones].

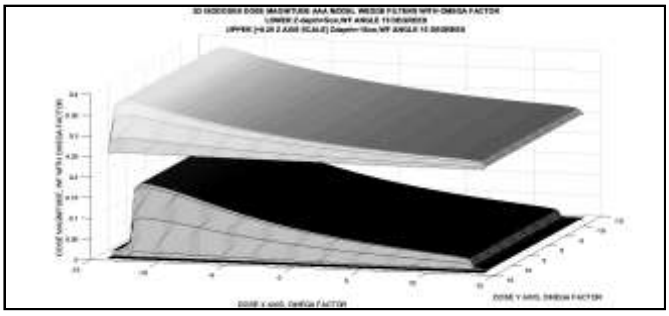

Figure 10.- [Grayscale imaging processing software] . For future implementation of BMs, a new 3D isodoses perspective in imaging-software developed from [85]. It is a Type I lateral-oblique imaging perspective of 3D Isodoses for z=5 cm [first], and z=15 cm [upper, scaled +0.25]. It is clear the height dose difference related to depth absorbed dose deposition. This Type I lateral imaging perspective of 3D Isodoses for z=15 cm [upper, scaled +0.25], and z=5 cm [lower] demonstrate the utility and innovation, [84], for TPO modern systems [Casesnoves, 2022]. It is sharp the dose difference magnitudes that can be get related to depth absorbed dose deposition. Dosimetry calculations,TPO, and photon-dose approximations can be carried out with these 3D Isodoses charts. Enhanced in Appendix.

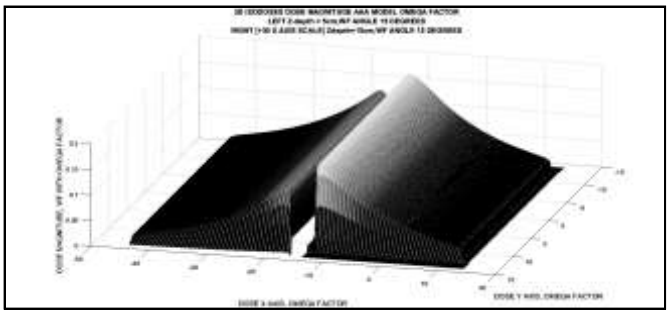

Figure 11.- [Grayscale imaging processing software] .For future implementation of BMs, a new 3D isodoses perspective in imaging-software developed from [85]. It is a Type II lateral imaging perspective of 3D Isodoses for z=5 cm [left], and z=15 cm [right, scaled +30]. It is clear the height dose difference related to depth absorbed dose deposition.

RADIOTHERAPY MEDICAL PHYSICS APPLICATIONS

Table 6 shows a resume of radiotherapy applications in head and neck tumors. Medical physics principal applications for radiotherapy TPO are explained briefly. Those prospective according to $N_{Effective}$ model applications are useful for radiotherapy research/applications on head and neck tumors and other types of cancer.

MODEL RESULTS APPLICATIONS FOR RADIOPROTECTION IN HEAD AND NECK TUMOR RT				
TYPE	**CLINICAL**	**RESEARCH**	**MIXED**	**COMMENTS**
BM Treatment planning optimization	TPO precise for head and neck tumors with BMs	TPO Modelling BMs developments according to $N_{Effective}$	Clinical improvements with BMs after research according to $N_{Effective}$	Inverse planning system set up on BMs according to $N_{Effective}$
LINAC OPTIMIZATION	Optimization of photon-dose for BMs	LINACs BMs Usage for IMRT, IMPT according to $N_{Effective}$	Exploration of new possibilities for $N_{Effective}$ models	Manufacturing adaptation of LINACs fro BMs according to $N_{Effective}$
Theoretical improvements for new models	Dosimetry improvements in accuracy according to radiobiology experimental $N_{Effective}$	From tumor survival clinical statistics advances in BMs according to $N_{Effective}$	According to $N_{Effective}$ new BMs research sources, both theory and clinical experimental trials	BMs got experimental evidences to be set on TPO according to $N_{Effective}$

Table 6.- Some radiotherapy and radioprotection applications for RT head and neck cancer treatment. TPO Medical Physics applications derive from this study results. Enhanced in Appendix.

DISCUSSION AND CONCLUSIONS

The objectives of the study were to apply artificial intelligence with GA Pareto-Multiobjective method for head and neck tumors BED model, Equation 1 , Table 4. The second objective was to apply Graphical Optimization on 3D $N_{Effective}$ clonogens population model in the same type of tumors, Table 5.

The PMO-BED model results can be considered acceptable. Simulations were presented as objective of the research, computationally designed for head and neck tumors [82] . This implementation of $N_{Effective}$ 3D model and corrections are useful for BED and Linear Quadratic optimal dose delivery magnitudes that will be developed in upcoming contributions [84]. It was intended to set in software precise experimental constants [22,81-84]. Therefore, 3D simulations could offer a realistic numerical image of $N_{Effective}$ clonogens population Fowler model for this type of cancer. Radiotherapy software improvements for new 3D Isodoses imaging processing results are detailed and shown in Figures 6-9. Numerical results at shown in Table 5.

Results for PMO-BED model comprise 2D GA Optimization imaging series, Figures 1-5, Table 4. Results for second model comprise 3D Graphical Optimization imaging series, Figures 6-9, and some maxima/minima numerical dataset, Table 5. According to literature experimental parameters [22,81-84], these 3D simulations can be considered acceptable. TPO applications for head and neck tumors are shown in Table 5. Results in invented/improved imaging 3D Isodoses charts in AAA dose-delivery with WF are presented in Figures 10-11.

Advantages of first model are the precision and adaptability of artificial intelligence GA method. Advantages for second model are accuracy in 3D determination of N_S and easy method from the presented models to calculate Clonogenes Survival Rates for head and neck tumors, getting improved radiotherapy TPO. Difficulties for the PMO-BED model are the rather longer running time compared to Inverse Least Squares optimization methods. Inconvenients for second one clonogens model, for example, are the experimental validation of the model, Equation 2, for large-scale clinical trials in head and neck cancers. Advantages of 3D Isodoses planning system images are extensive in TPO calculations and modern imaging-guided RT treatment.

Grosso modo, Pareto Multiobjective model was got applied for optimization of radiotherapy BED algorithm. For the second model, $N_{Effcetive}$ algorithms were implemented to refine the $N_{Survival}$ magnitude determination to be set in BMs. The consequence is an improved radiation therapy treatment for head and neck RT oncology. Applications on 3D Isodose charts for AAA model TPO with WF in radiation therapy were upgraded and shown.

SCIENTIFIC ETHICS STANDARDS

GA Artificial intelligence software was developed originally by Dr Casesnoves on September 2022. All initial modelling equations were developed from previous researchers contributions [22-25]. The N_S initial formulation and integral Tumor Control Cumulative Probability, (TCCP), were published in [22-25]. From those equations, all the mathematical development implementation is original from the author [1-21,75]. This article has previous papers mathematical techniques, reviews with explanations, [1-21, 75], whose use was essential to make model numerical solutions and approximations. Equation 2 and $N_{Effective}$ model are developed and reviewed from [20,21,75,85],

essential for study understanding. Some information of [20,2175,85] was presented for results clarification. The number of Dr Casesnoves publications at references is intended also for reader's learning. This study was carried out, and their contents are done according to the European Union Technology and Science Ethics and International Scientific Ethics norms [38,43-45]. This research was completely done by the author, the calculations, images, mathematical propositions and statements, reference citations, and text is original from the author. When a mathematical statement, proposition or theorem is presented, demonstration is always included. If any results inconsistency is found after publication, it is clarified in subsequent contributions. When a citation such as [Casesnoves, 'year'] appears, there is not vanity or intention to brag. The reason is to keep clearly the intellectual property. The article is exclusively scientific, without any commercial, institutional, academic, religious, religious-similar, non-scientific theories, personal opinions, friends and/or relatives favours, political ideas, or economical influences. When anything is taken from a source, it is adequately recognized. Ideas and some text expressions/sentences from previous publications were emphasized due to a clarification aim [38,43-45].

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AUTHORS' BIOGRAPHY

Dr Francisco Casesnoves earned the Engineering and Natural Sciences PhD by Talllinn University of Technology (started thesis in 2016, thesis Defence/PhD earned in December 2018, official graduate Diploma 2019). Dr Casesnoves is European Union and Internationally qualified as Doctor in Engineering to supervise PhD Theses, Master Theses, and Bachelor Theses in science and engineering. He works as independent research scientist in computational-engineering/physics. Dr Casesnoves earned MSc-BSc, Physics/Applied-Mathematics (Public Eastern-Finland-University, MSc Thesis in Radiotherapy Treatment Planning Optimization, which was developed after graduation in a series of Radiation Therapy Optimization-Modelling publications [2007-present]). Dr Casesnoves earned Graduate-with-MPhil, in Medicine and Surgery [1983] (Madrid University Medicine School, MPhil in Radioprotection Low Energies Dosimetry [1985]). He studied always in public-educational institutions, was football player 1972-78 (defender and midfielder) and as Physician, supports healthy life and all sports activities. Casesnoves resigned definitely to his original nationality in 2020 for ideological reasons, democratic-republican ideology, ethical-professional reasons, anti-state monarchy corruption positions, and does not belong to Spain Kingdom anymore. His constant service to the International Scientific Community and Estonian technological progress (2016-present) commenced in 1985 with publications in Medical Physics, with further specialization in optimization methods in 1997 at Finland—at the moment approximately 100 recognized publications with approximately 65 DOI papers. His main branch is Computational-mathematical Nonlinear/Inverse Methods Optimization. Casesnoves best-achievements are the Numerical Reuleaux Method in dynamics and nonlinear-optimization [books 2019-2020], The series of Radiotherapy Improvements for AAA superposition-convolution model, the Graphical and Interior Optimization Methods [2016-8], the new Computational Dissection-Anatomical Method, [2020], invention of Forensic Robotics [2020-2021], invention of 3D Isodoses in radiotherapy TPO, and Molecular Effect Model for High Temperature Superconductors [2020]. Dr Casesnoves PhD thesis is an Estonian scientific service to European Social Fund and several EU Research Projects. Dr Casesnoves scientific service since 2016 to the Free and Independent Republic of Estonia for technological development (and also at Riga technical University, Power Electrical and Electronics Department) is about 40 physics-engineering articles, two books series, and 1 industrial radiotherapy project associated to Europe Union EIT Health Program (Tartu University, 2017).

APPENDIX

This Appendix shows the most important Tables Figures to demonstrate the results sharply.

$N_{Effective}$ MODEL FOR HEAD AND NECK TUMORS APPLICATIONS	
RT TPO METHOD IMPROVEMENTS	**DIRECT EFFECT**
Mathematical Improvements when N_{Eff} is implemented in Survival Fraction Models	With N_{Eff} Implementation TCP is numerically more accurate Without N_{Eff} TCP is falsely numerically higher With N_{Eff} Implementation NTCP is numerically more accurate Without N_{Eff} Implementation NTCP is falsely numerically lower
N_{Eff} Implementation in Survival Fraction Models	Dose Delivery Precision because it minimizes Clonogenes growth during radiotherapy Treatment Time, Maximum Effect/Maximum Tumor Control Probability [TCP]
N_{Eff} Implementation in Survival Fraction Models for exact calculation of NTCP instead N_0 . Then, TCP and NTCP are more efficacious.	Radioprotection OARs Dose Precision because it sets exact Clonogenes growth during radiotherapy Treatment Time, Maximum Effect/Maximum Normal Tissue Complications Probability [NTCP]
Optimization of Biological Models	Dose Delivery Precision, minimum dose/ maximum effect
Previous Photon-dose Optimization	Dose Delivery Precision to be implemented in BM, minimum dose/ maximum effect
Normal Tissue Complications Probability Models [NTCP]	Dose-Volume-Histogram Dose Delivery Precision to be implemented in BM, minimum dose at OARs
ON PATIENT EFFECTS	
OARs Radioprotection	Avoid Damage at any FSUs [Organ Funcional Subunits]
Radiation Therapy Secondary Effects	Hypo Fractionations decreases Radiation Undesirable Symptoms
Patient Life Quality	Not only Physical benefit but also Psychological for Patient

Table 1. [enhanced].-Brief of RT TPO methods and subsequent positive effects in patient cure and post-radiation life. Those are justified also for the rise of head and neck tumor survival time and complete cure got by modern RT, IMRT, IMPT, Chemo, and Inmunotherapy advances. Enhanced in Appendix.

HEAD AND NECK TUMORS CLONOGEN REPOPULATION DURING TREATMENT RT TIME MODEL DATASET FOR SIMULATIONS		
PARAMETER	**COMPUTATION INTERVAL**	**DETAILS**
HEAD AND NECK TUMOR N_0	[10^3 , 10^{11}] clonogens	This interval was selected from [22,80,81,83]
T Standard RT Time	Fixed days [22,46]	This interval was selected from [22,80], However it varies according to authors [25], depending on Conventional, Hiper or Hypo Fraccionated RT treatment time
T_{Delay}	Fixed days, when clonogens start mitosis	It was supposed weekends or hospital break days and unpredictable delays [80,81,83]
HEAD AND NECK TUMOR $T_{Potential}$	$T_{Potential}$ ϵ [5,6] days ; [80,81,83]	Head and Neck cancer in vivo data selected from [80,81,83]

Table 2 [enhanced] .- Second model for clonogens. Computational dataset from [19,21-25,74,80,81] .

$N_{Effective}$ MODEL MATLAB SOFTWARE METHOD(S)		
COMPUTATIONAL OBJECTIVE	**PROGRAMMING DEVELOPMENT**	**COMMENTS**
Implementation of experimental parameters for T_{Delay} , $T_{Potential}$,N_0	Precision required to get true simulations for head and neck tumors	Those parameters differ for every type of tumor
Optimization of implementation of $N_{Effective}$ for fast running time and imaging quality	Precision required to organize and optimize correct order, loops, patterns, and exactitude of every imaging processing subroutine	It is necessary to select the most appropriate subroutine, among several imaging processing sources for getting good 3D charts
Imaging processing refinement	Logarithmic scale changes were necessary because of the high numerical magnitude of some parameters	Several imaging processing solutions can be used.
Imaging processing matrices size optimization for final 3D plots	To get good-quality 3D model images it is necessary optimize, select, and order the best imaging-tiles matrices size combination linked to imaging processing tools	Not always bigger tiles number implies better imaging quality

Table 3 [enhanced] .- $N_{Effective}$ model main parameters for 3D Graphical simulations [1-20, 74] . Program software parts numerically calculated for Equations 1-3. The data/method from Tables 2-3 was implemented.

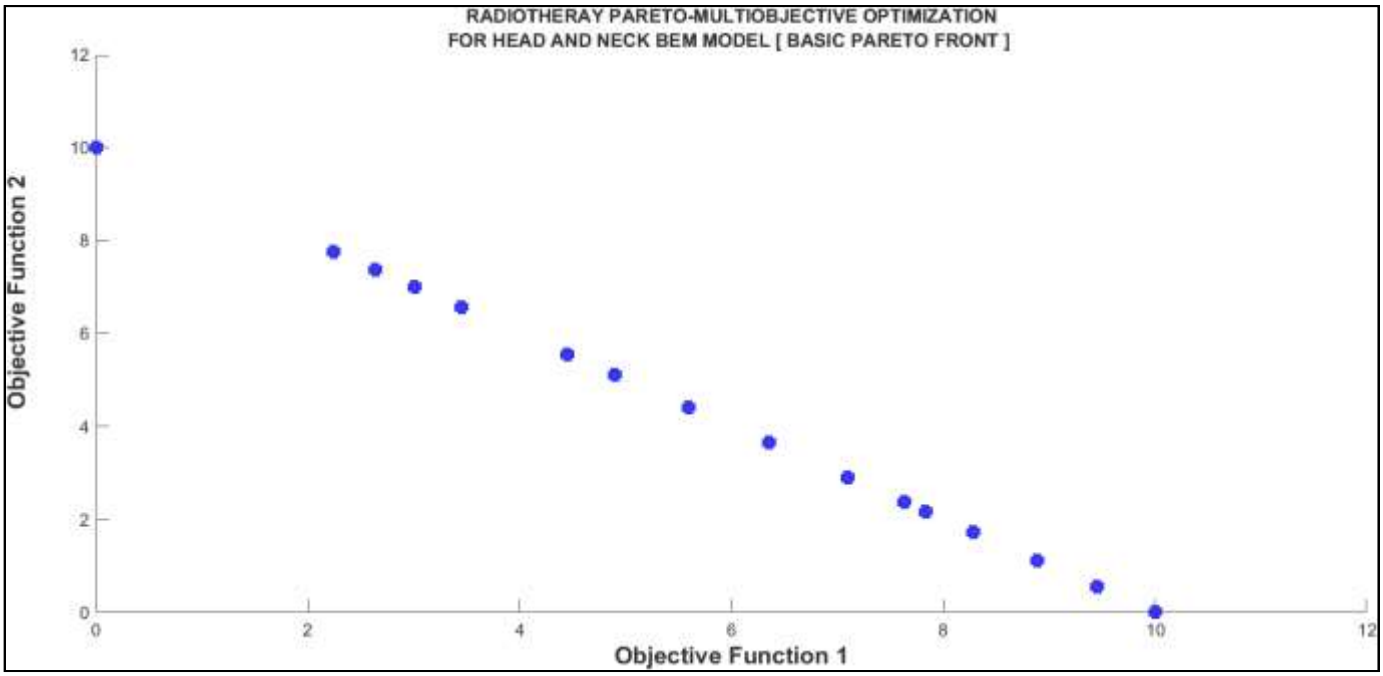

Figure 1 [enhanced].-This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f_1 and f_2 show low residuals. The number of points on the Pareto front was: 18. The number of generations was : 300. Therefore, results are acceptable.

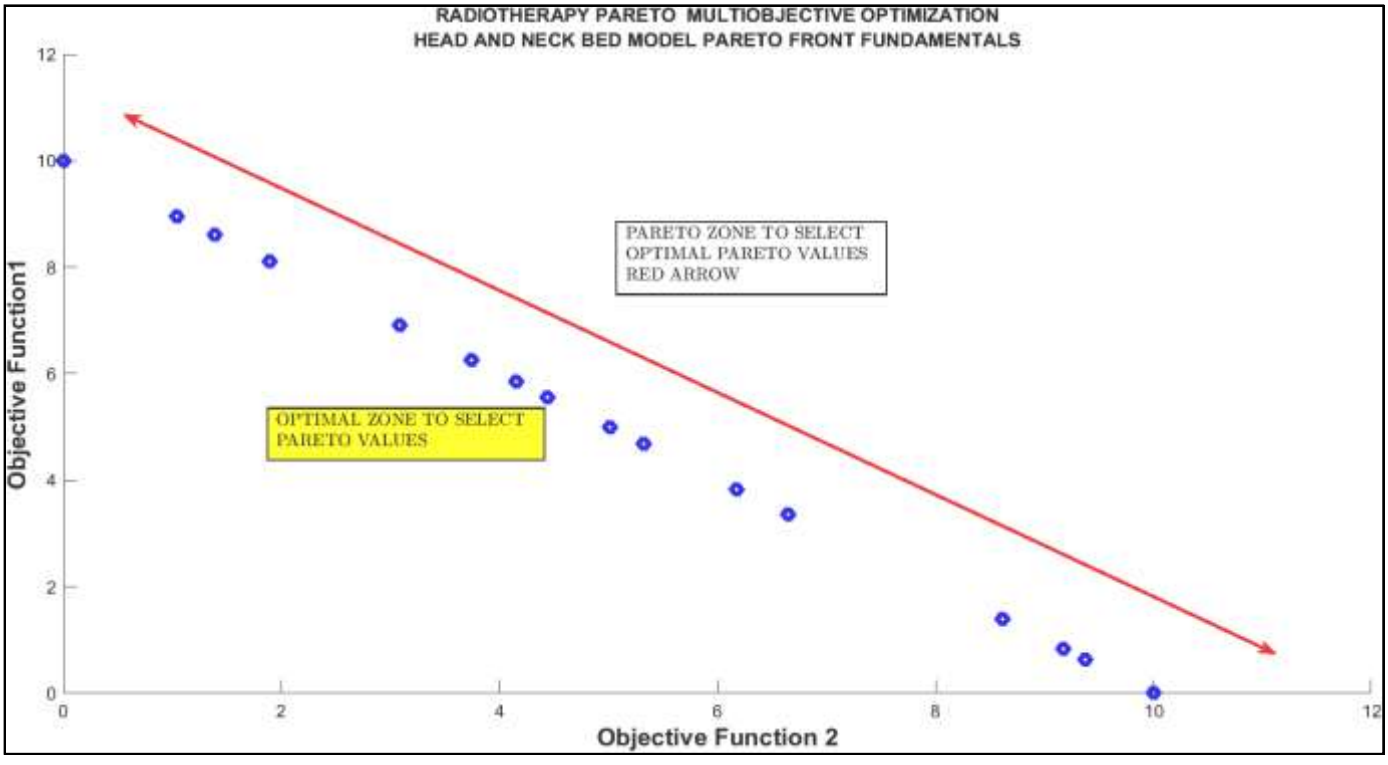

Figure 2 [enhanced] .- This is the lined-marked inset graph showing the Pareto Front. Since the number of functions calculated is quite high, the points that show the distance vary significantly for 300 generations. The fundamentals of PMO calculations are usually based on 2D PMO functions charts. In this study both Objective f_1 and f_2 that show low residuals. Note the selection for best pareto values.

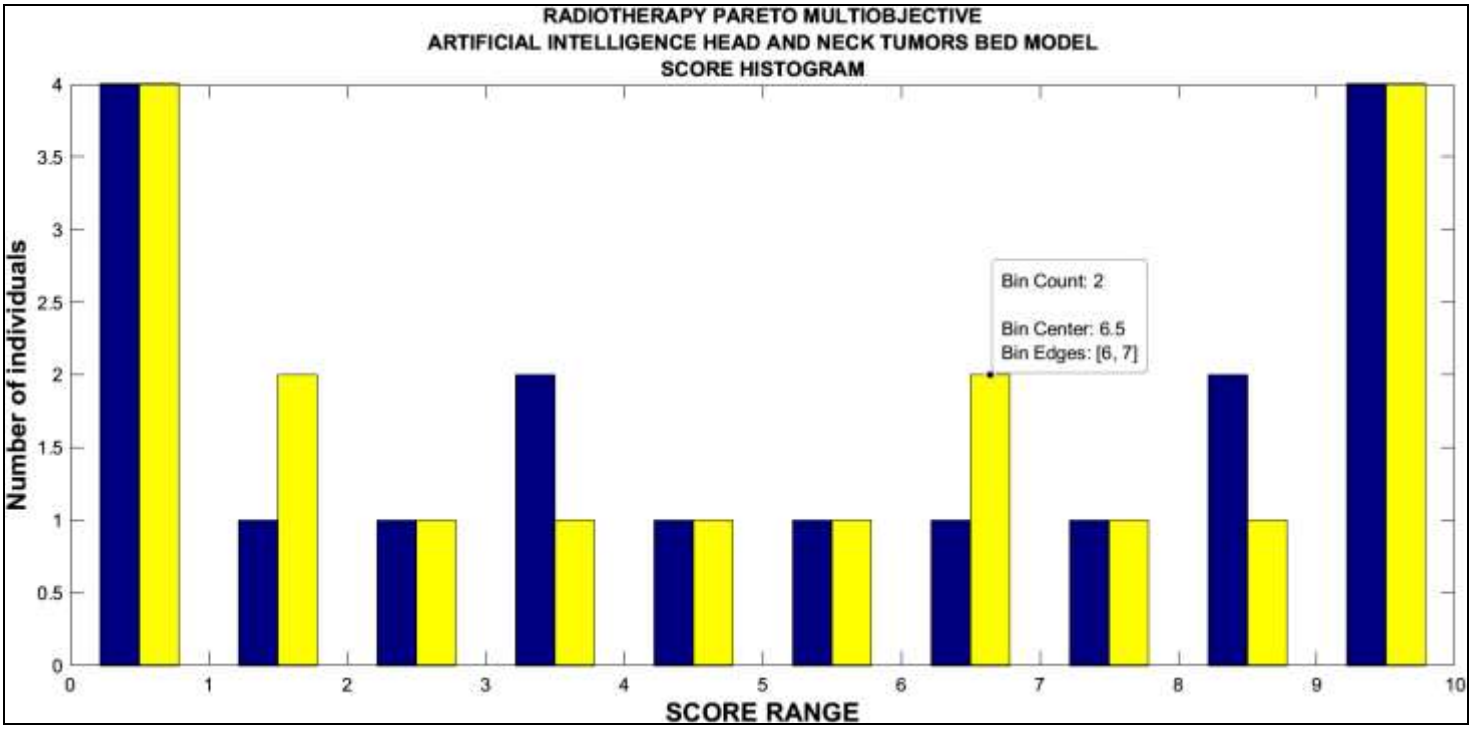

Figure 4 [enhanced].- Complementary 2D graphs showing that 100% criteria is met and number of individuals paired-histograms versus score range. Objective f_1 and f_2 are differentiated by blue and yellow colors.

BRIEF OF NUMERICAL RESULTS FOR PMO OPTIMIZATION WITH GA FOR HEAD AND NECK TUMOR BED MODEL	
PARAMETER	INTERVAL OPTIMIZATION RESULT
OPTIMAL HYPERFRACTIONATION DOSE Gy	[1.163 , 1.3415] Gy
OPTIMAL TIME TREATMENT AFTER STANDARD 21 DAYS	[18 , 20] Days (after 21 standard days)
OPTIMAL DOSE FRACTIONS NUMBER	[38 , 50]
The number of points on the Pareto front was: 18 The number of generations was : 300	

Table 4 [enhanced].- Brief of PMO Artificial Intelligence with GA optimization numerical results in Head and Neck tumors for advanced TPO.

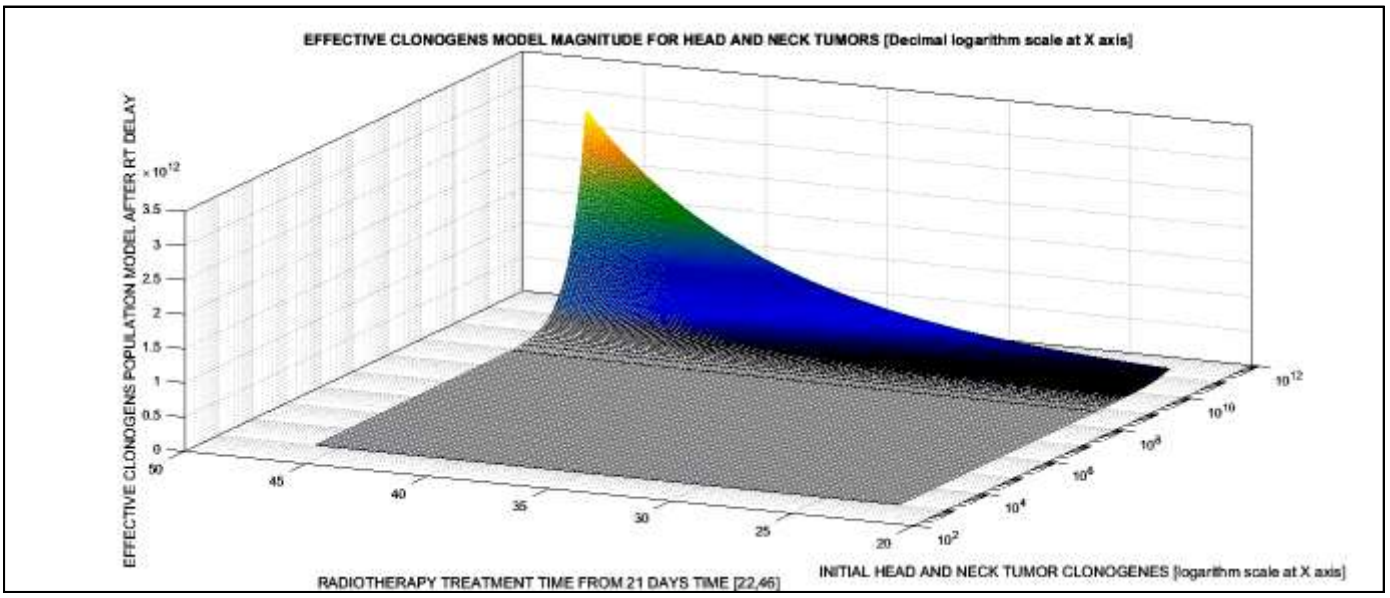

Figure 6 [enhanced].- $N_{Effective}$ Rate simulation 3D image for head and neck tumors. At X axis, logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The image processing perpective was set to demonstrate the almost exponential/parabolic increase of $N_{Effective}$ magnitude from clonogenes population approximate value 10^8 . The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [100-250 x 100-250] elements. At figure, inset, axes interval modifications explained.

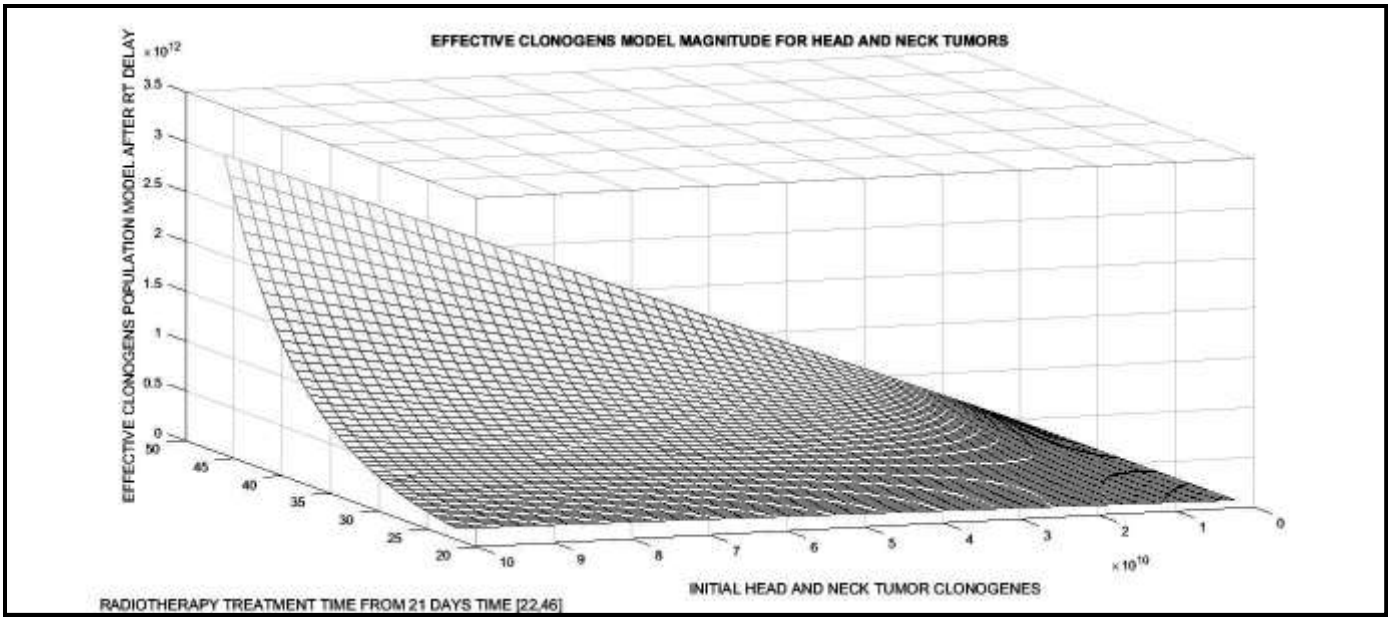

Figure 4 [enhanced] .- Grayscale-processed with magnitude boxes Matlab $N_{Effective}$ Rate simulation. 3D image for head and neck tumors shown. Image was set without any logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The grayscale image processing perpective was set to demonstrate the almost exponential/parabolic increase of $N_{Effective}$ magnitude from clonogenes population approximate value 10^8 . The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [100-250 x 100-250] elements. At figure, inset, axes interval modifications explained.

NUMERICAL RESULTS FOR $N_{Effective}$ MODEL IN HEAD AND NECK TUMORS					
Minimum [N_0] Minimum [T_{Delay}]	Minimum [$N_{Effective}$] Minimum [T_{Delay}]	Maximum [N_0] Minimum [T_{Delay}]	Minimum [$N_{Effective}$] Maximum [T_{Delay}]	Maximum [N_0] Maximum [T_{Delay}]	Maximum [$N_{Effective}$] Maximum [T_{Delay}]
1000 1.49 days	1117 1.49 days	1.00×10^{11} 1.00 days	3.01×10^{4} 27-28 days	1.00×10^{11} 27-28 days	3.01×10^{12} 27-28 days

Table 5 [enhanced] .- Some Maxima and Minima of Numerical results for second clonogens model model parameters.

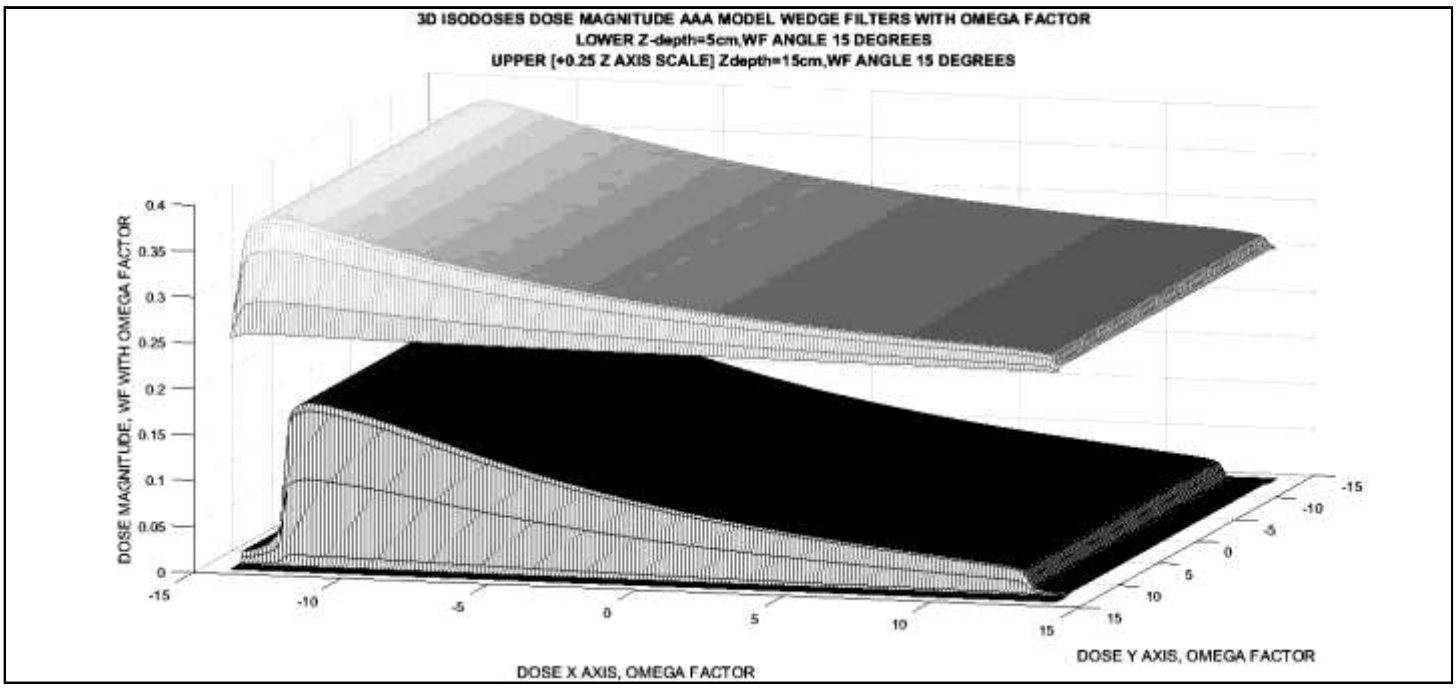

Figure 8 [enhanced].- [Grayscale imaging processing software] . For future implementation of BMs, a new 3D isodoses perspective in imaging-software developed from [85]. It is a Type I lateral-oblique imaging perspective of 3D Isodoses for z=5 cm [first], and z=15 cm [upper, scaled +0.25]. It is clear the height dose difference related to depth absorbed dose deposition. This Type I lateral imaging perspective of 3D Isodoses for z=15 cm [upper, scaled +0.25], and z=5 cm [lower] demonstrate the utility and innovation, [84], for TPO modern systems [Casesnoves, 2022]. It is sharp the dose difference magnitudes that can be get related to depth absorbed dose deposition. Dosimetry calculations,TPO, and photon-dose approximations can be carried out with these 3D Isodoses charts.

MODEL RESULTS APPLICATIONS FOR RADIOPROTECTION IN HEAD AND NECK TUMOR RT				
TYPE	**CLINICAL**	**RESEARCH**	**MIXED**	**COMMENTS**
BM Treatment planning optimization	TPO precise for head and neck tumors with BMs	TPO Modelling BMs developments according to $N_{Effective}$	Clinical improvements with BMs after research according to $N_{Effective}$	Inverse planning system set up on BMs according to $N_{Effective}$
LINAC OPTIMIZATION	Optimization of photon-dose for BMs	LINACs BMs Usage for IMRT, IMPT according to $N_{Effective}$	Exploration of new possibilities for $N_{Effective}$ models	Manufacturing adaptation of LINACs fro BMs according to $N_{Effective}$
Theoretical improvements for new models	Dosimetry improvements in accuracy according to radiobiology experimental $N_{Effective}$	From tumor survival clinical statistics advances in BMs according to $N_{Effective}$	According to $N_{Effective}$ new BMs research sources, both theory and clinical experimental trials	BMs got experimental evidences to be set on TPO according to $N_{Effective}$

Table 6 [enhanced] .- - Some radioprotection for RT head and neck cancer TPO Medical Physics study applications derived from results.