Variable RBE in proton therapy: Comparison of model predictions and their influence on clinical-like scenarios

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Introduction

- Charged particles are densely ionizing
  → higher cell killing rate compared to photons
- RBE concept: $\mathbf{RBE = (D_x/D_{ion})|_{end\ point}}$

RBE = f (Physical params (particle type, dose level, LET)
Biol. params (tissue type, end point, cell cycle phase, oxygen. level))

RBE for proton therapy:

ICRU recommendation: constant RBE of 1.1

- approximation → supported by fact that available biological data is insufficient to justify clinical usage of other proposed approaches
- recent review of experimental data (Paganetti 2014): trend of increase in RBE for low $(\alpha/\beta)_x$ at low dose levels

Model Selection

Purpose: For three selected, different radiobiological models:

- Compare their parameter predictions
- Compare their impact on clinical-like scenarios

Criteria: Both phenomenological and biophysical models:

- Different trends for β as f(LET)
- No plan dependencies

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(1) Local Effect Model IV* (**LEM**) – Biophysical Model

- Link biological response to double strand breaks pattern
- β decreases with LET
- Concept of D_t (transition dose: $S(D_t)_x$ exp → linear)
- Coupled to FLUKA MC code in HIT MC framework**

→ validated with p and He beams for different cell lines***

Elsässer 2010 Int J Rad Onc 78, Friedrich 2012 Int J Rad Biol 88, Krämer Scholz 2006 PMB 51, * Mairani 2010 PMB 55, **Mairani 2013 PMB 58*

Model Selection

(2) Carabe-Fernandez* (**CAR**) - Phenomenological

β increases with LET → concept of $RBE_{min,max} = f(LET, \ldots)$, asymptotic values of RBE at $D \rightarrow \infty$ / 0

→ Validated for V79 cells at $(\alpha/\beta)_x$ = 2.686 Gy

(3) Wedenberg** (**WED**) - Phenomenological

α/α_x increases linearly with LET *(up to 30 keV/µm),* slope inversely proportional to $(\alpha/\beta)_x$; β constant: $\beta = \beta_x$

→ model hypotheses tested on wide set of experimental data:

$(\alpha/\beta)_x$ = (2.7 ..70) Gy;

LET = (6 … 30) keV/µm

**Carabe-Fernandez 2007, Int J Rad Biol 83*
***Wedenberg 2013, Acta Oncol 52*

Material & Methods

(a) Model predictions:

- α and β parameters as f(LET) (various $(\alpha/\beta)_x$, D_t)
- RBE as a f(LET) (various $(\alpha/\beta)_x$, D_t, D_x)
- RBE as a function of proton dose D (various $(\alpha/\beta)_x$, D_t, LET)

Parameter variation:

- **$(\alpha/\beta)_x$** = 2 Gy / 10 Gy (late/early responding tissue)
- **D_x** = 2 Gy / 4 Gy (reference photon dose levels)
- **D_t** = 10 Gy, 40 Gy (transition dose values for LEM)
- **LET** = 1 keV/µm, 6.5 keV/µm (low/high)

(b) Monte Carlo calculation:

- FLUKA Monte-Carlo code
- Scoring: physical dose, LET_D (WED, CAR) or D_{RBE} (LEM)

Material & Methods

(c) SOBP in water:

- Single field, D = 2 Gy(RBE)
- 150 x 90 x 40 mm³ @ 76mm depth (center)

→ depth dose profiles and lateral RBE profiles

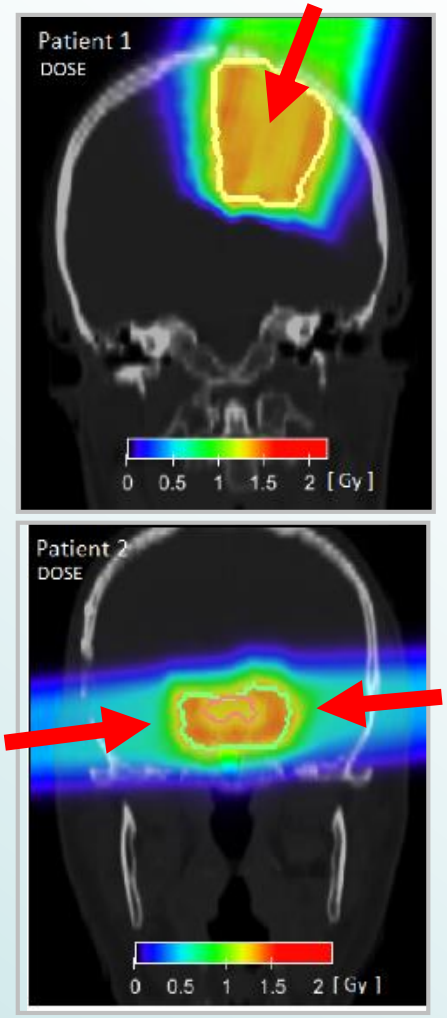
(d) Two clinical cases:

- Cranial indications, 27 x 2 Gy(RBE)
- Single field / homogeneous region
- Two opposite fields / complex region

→ LET and D_{RBE} distributions, D_{RBE}VHs, LETVH

→ Biological range shift (Δ) maps in BEV

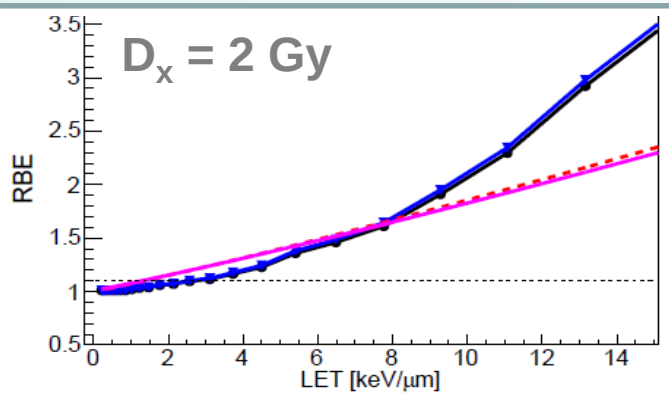
($\Delta = R_x(RBE_{var})-R_x(RBE=1.1)$, with x = (90/80/50)%)

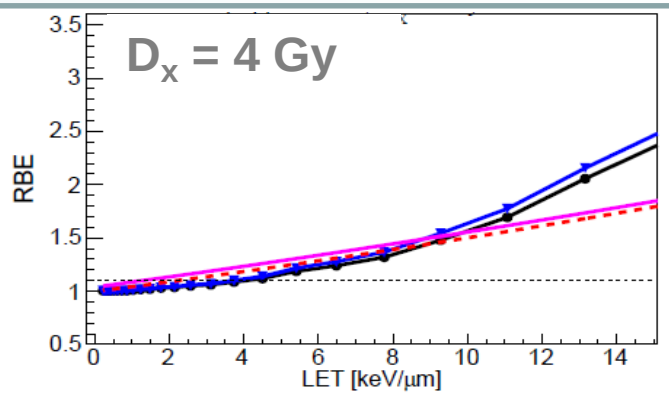


Model Comparison – RBE(LET)

$(\alpha/\beta)_x$ = 2 Gy

LEM-10
LEM-40
WED
CAR
RBE=1.1 …

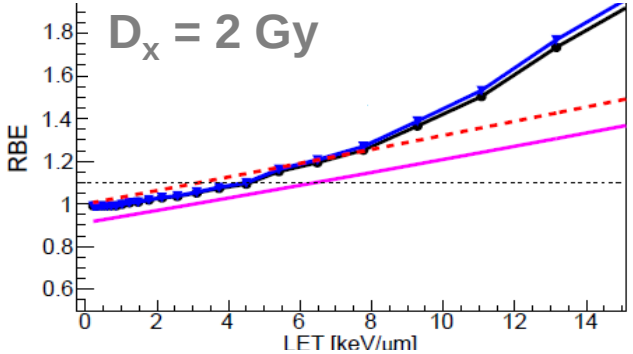


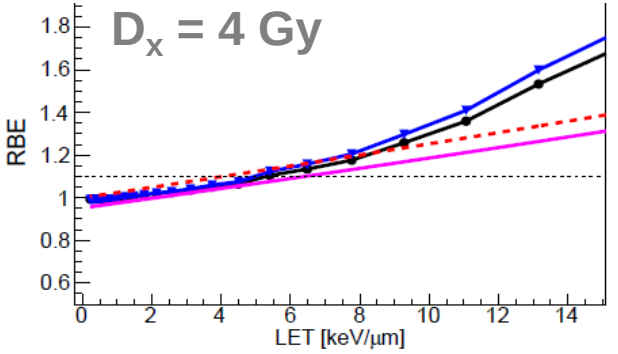


- RBE: increases with LET (in analyzed range), decreases with increasing D_x, increases for decreasing $(\alpha/\beta)_x$
- similar RBE values up to ~ 8 keV/µm

$(\alpha/\beta)_x$ = 10 Gy

LEM-10
LEM-40
WED
CAR
RBE=1.1 …



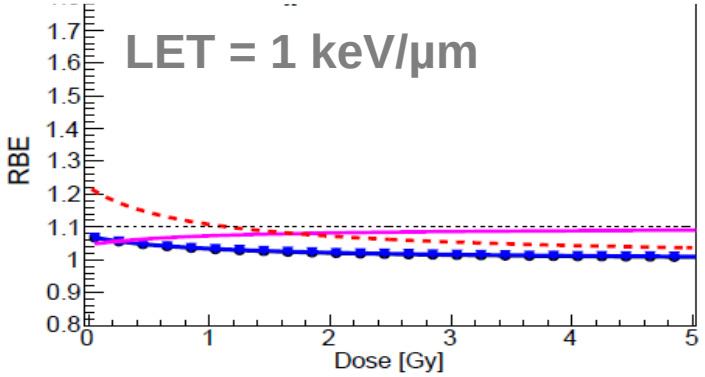


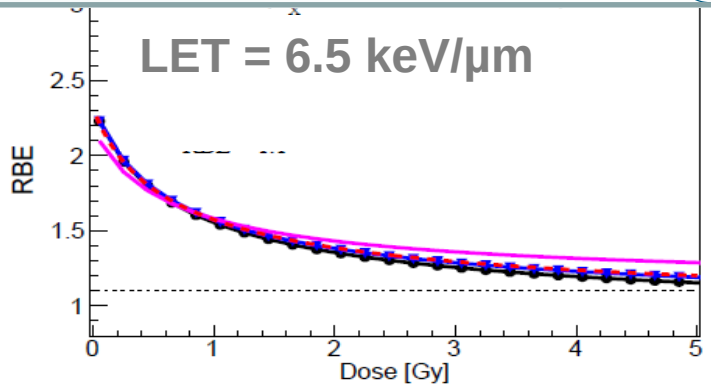
- similar RBE values up to ~ 8 keV/µm for LEM and WED
- CAR RBE<1 for low LET

Model Comparison – RBE(D)

$(\alpha/\beta)_x$ = 2 Gy

LEM-10
LEM-40
WED
CAR
RBE=1.1 …

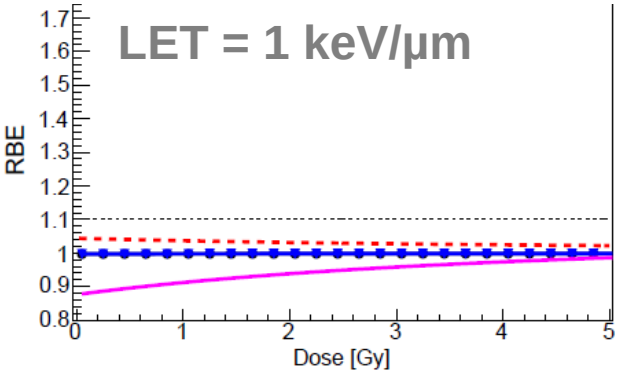


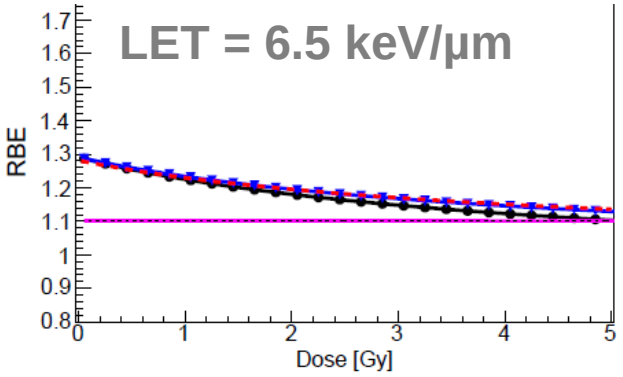


- **Low LET:** LEM, WED: RBE ↑ for dose ↓, CAR: slight RBE ↓ for dose ↓
- **High LET:** RBE ↑ for dose ↓ (all); RBE > 1.1 (≤ 2.3 @ very low doses)

$(\alpha/\beta)_x$ = 10 Gy

LEM-10
LEM-40
WED
CAR
RBE=1.1 …

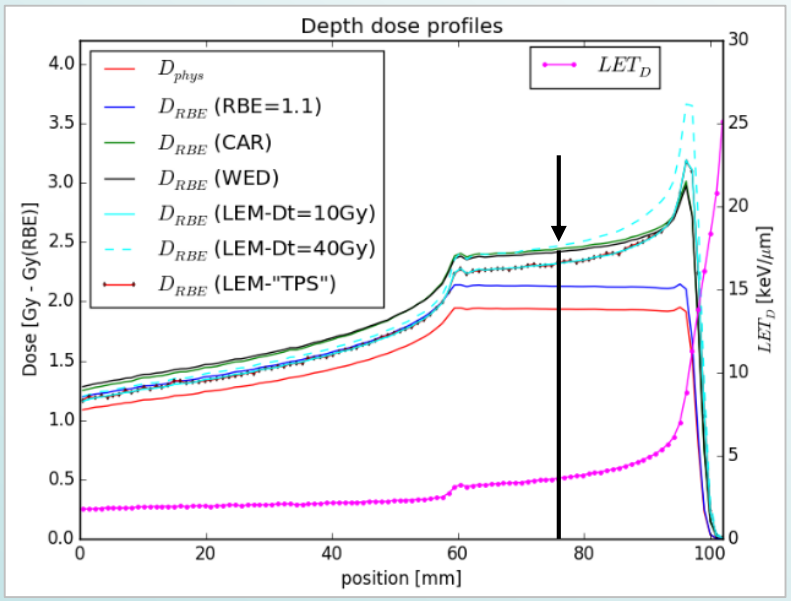


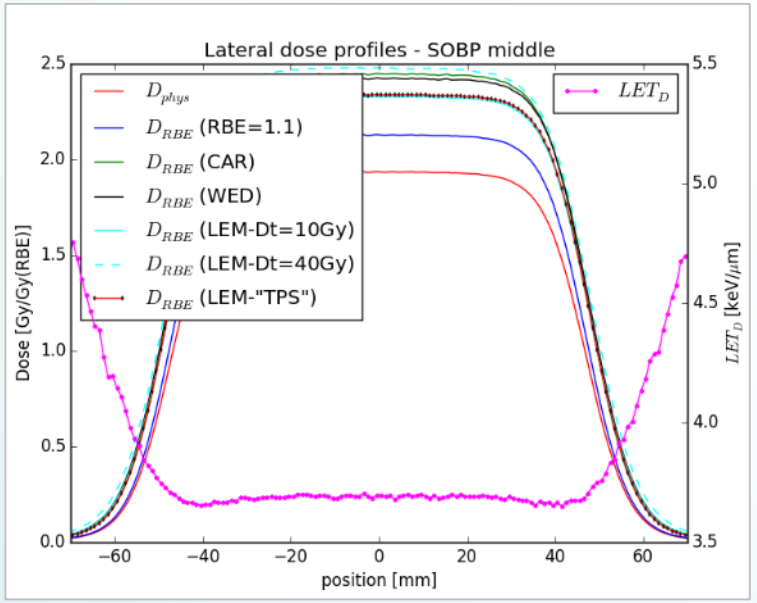


- **Low LET:** WED: RBE ↑ for dose ↓, LEM: RBE ~ const
- **High LET:** RBE ↑ for dose ↓ (WED/ LEM); RBE > 1.1 (≤ 1.3 @ very low doses)
- CAR: if $RBE_{max} < RBE_{min} \rightarrow$ RBE ↑ for dose ↑

Results – SOBP

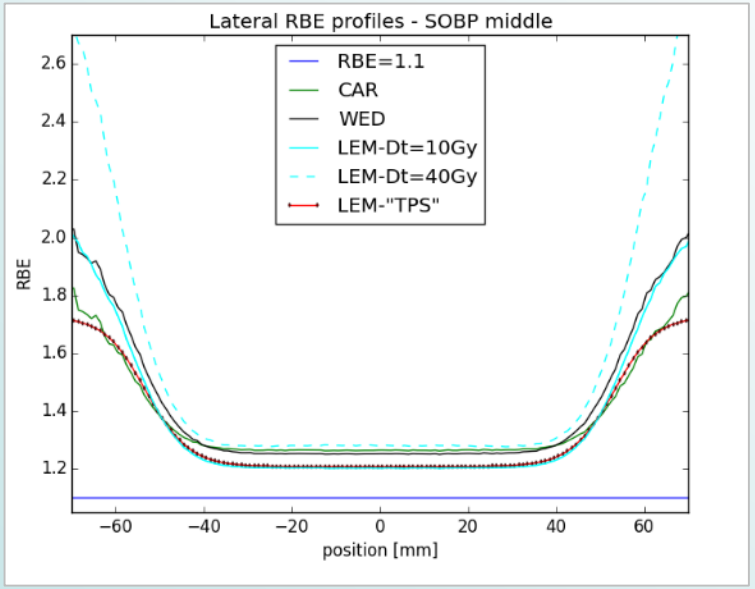
$(\alpha/\beta)_x$ = 2 Gy





DDD: RBE @ entrance / middle of SOBP:

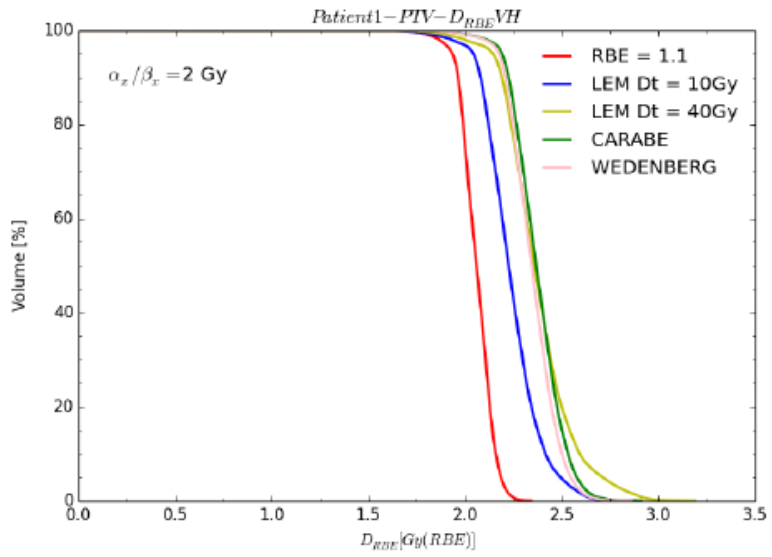
- WED: 1.20 / 1.31
- CAR: 1.17 / 1.31
- LEM10: ~1.1 / >WED/CAR @ last mm

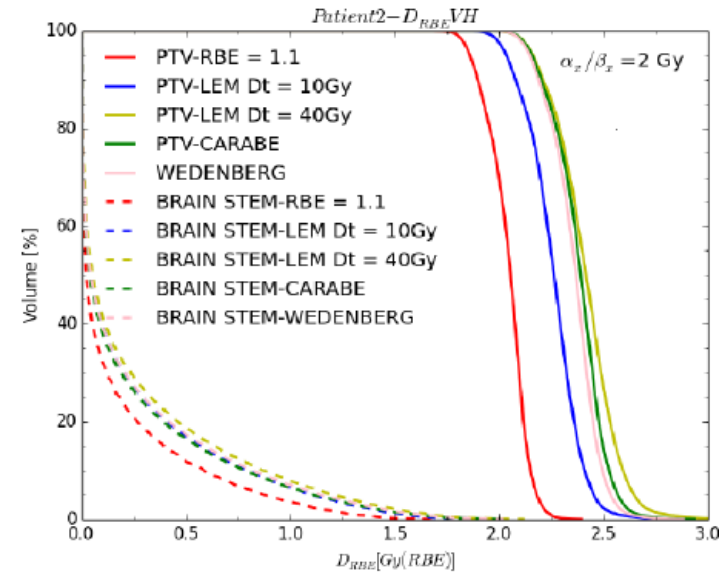


Lateral RBE profiles:

- Plateau: RBE(CAR/WED) > RBE(LEM)
- (80-20)% fall-off: ~1mm widening (all)

Patient Cases





$(\alpha/\beta)_x$ = 2 Gy

LET_D:

- P1:
  $LET_{95\%(<5\%)}$ ~ 5.0 (8.1) keV/µm
  hot area distal to PTV
- P2:
  $LET_{95\%(<5\%)}$ ~ 4.5 (6.5) keV/µm
  hot distal edges smeared out

D_{RBE} (D_{presc} = 2 Gy(RBE)):

- P1:
  $D_{mean,\ varRBE}$ = (2.23 - 2.38) Gy(RBE)
- P2:
  $D_{mean,\ varRBE}$ = (2.26 - 2.41) Gy(RBE)

→ CAR/WED/LEM40 similar values

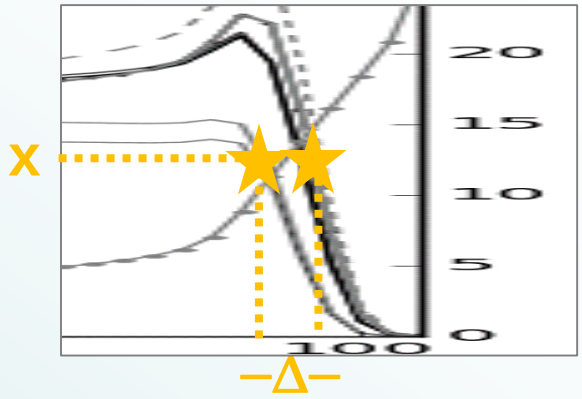
(for $(\alpha/\beta)_x$ = 10 Gy: dose values close to RBE = 1.1 values)

Biological Range Shift

Biological range shift in BEV:

$$\Delta = R_x(RBE_{var}) - R_x(RBE=1.1)$$

with x = (90/80/50)% of D_{presc}



Δ (80% D_{presc}) [mm] - $(\alpha/\beta)_x$ = 2 Gy		
Model	**Patient 1**	**Patient 2**
LEM (D_t = 10 Gy)	4.3	3.0
LEM (D_t = 40 Gy)	5.4	4.4
WED	3.6	3.6
CAR	3.5	3.4

- Values found between (3.0-5.4) mm
- Increasing D_t for LEM → larger range shifts

(for $(\alpha/\beta)_x$ = 10 Gy: range shifts (0.6-2.4)mm)

Summary

Model comparison:

- Models predict similar dependencies for RBE up to ~8 keV/µm
- Identified restrictions for validity of CAR model

Clinical application:

- LET distribution strongly dependent on field configuration
- Mean D_{RBE}(PTV) enhanced by ≥10% for all models at low $(\alpha/\beta)_x$
- Range shifts of up to 5mm; models show similar behaviour
- Lateral widening could be an issue as well

→ potential dose enhancement and range shift for variable RBE

→ strong suggestion to consider variable RBE in proton therapy TP

→ simple models sufficient for initial guess

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Backup


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RON MORGAN
"Oh, the magic carpets are just for backup."

LEM in FLUKA

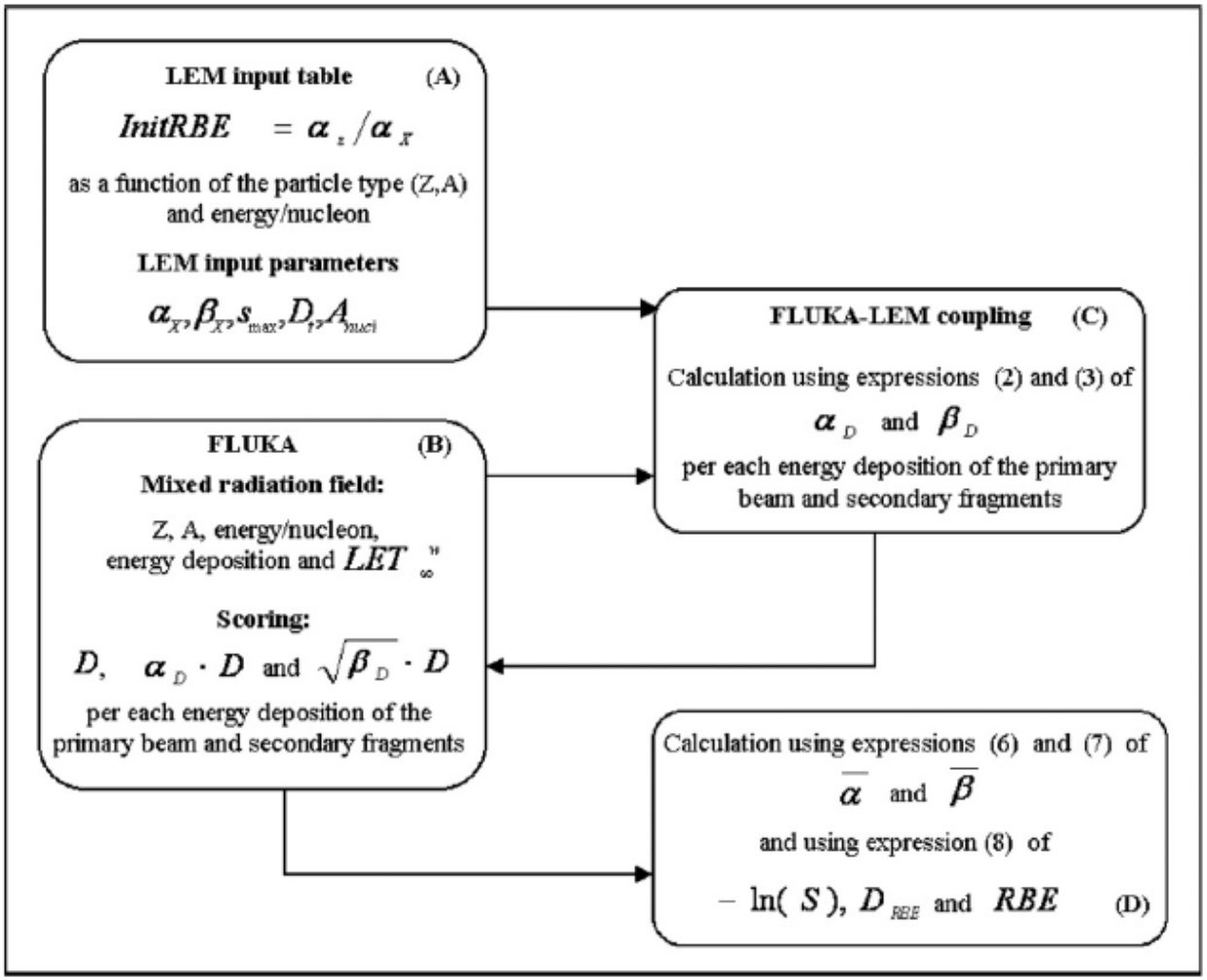

Figure 1. Schematic representation of the coupling of the FLUKA MC code with the LEM.

Parameters

Table 1. Photon parameters used for the two representative tissues for low and high $(\alpha/\beta)_x$.

α_x [Gy^{-1}]	β_x [Gy^{-2}]	$(\alpha/\beta)_x$ [Gy]	D_t [Gy]
0.123	0.0616	2	10, 40
0.616	0.0616	10	10, 40

Wedenberg:

$$RBE = -(\alpha/\beta)_x/2/D + 1/D * sqrt(0.25*(\alpha/\beta)_x^2 + (0.434*LET + (\alpha/\beta)_x)*D + D^2)$$

Carabe:

$$RBE = -(\alpha/\beta)_x/2/D + 1/D * sqrt\{0.25*(\alpha/\beta)_x^2 + (\alpha/\beta)_x*D*(0.834 + 0.154*2.686/(\alpha/\beta)_x*LET) + D^2*(1.09 + 0.006*2.686/(\alpha/\beta)_x*LET)^2\}$$

Results – Patient Cases - D_{RBE}