The therapeutic potential of FLASH-IOERT

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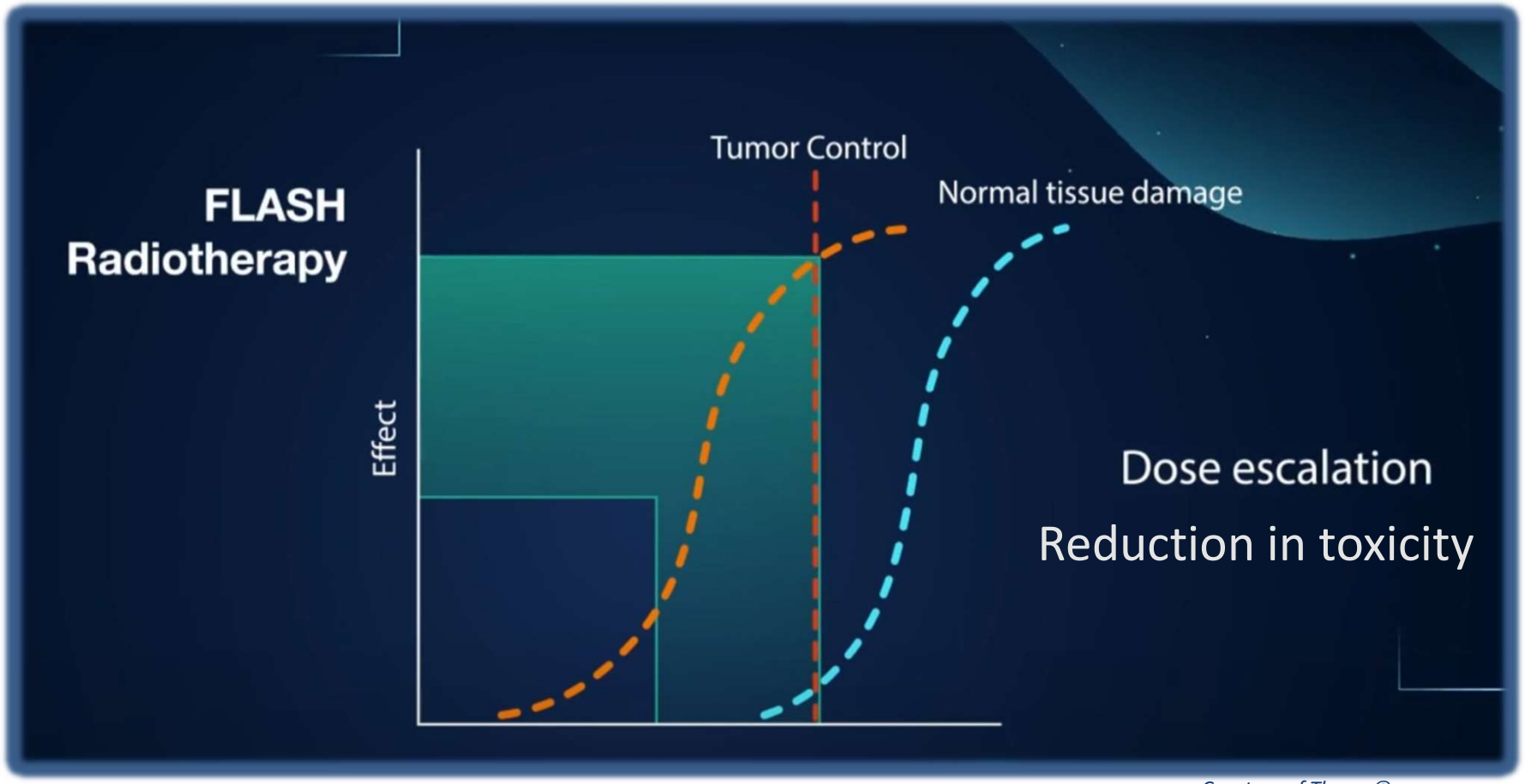
Introduction to FLASH EFFECT



Courtesy of Theryq©

Introduction to FLASH EFFECT

PHOTONS

Synchontron

NOT available in clinical practice

PROTONS

Cyclotron

Available in clinical practice
Useful for deep-seated tumours

ELECTRONS

(Mobile) LINAC

Available + in clinical practice
Useful for superficial tumours

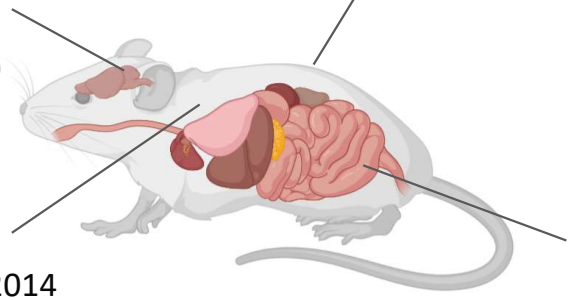
Introduction to FLASH EFFECT

FLASH-RT limits radiation induced-toxicities while being isoeffective on tumors compared to conventional-RT

Brain :
Montay-Gruel et al. 2017

Simmons et al. 2019
Allen et al. 2020
Montay-Gruel et al. 2020
Alaghband et al. 2020

Skin :
Field et al. 1974
Inada et al. 1980
Soto et al. 2020



Lung :
Favaudon et al. 2014

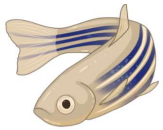
Fouillade et al. 2020

Gut :
Levy et al. 2020

Ruan et al. 2021

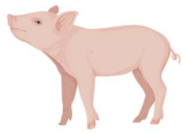
Electrons

Schoenauen al. 2024



Montay-Gruel et al. 2019

Vozenin et al. 2019
Rohrer Bley et al. 2022



Vozenin et al. 2019
Rohrer Bley et al. 2022

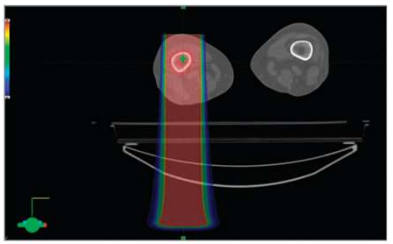
Kondradsson et al. 2021

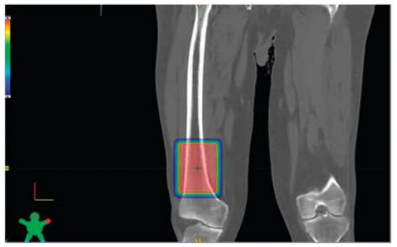
FLASH EFFECT : clinical trials on humans

First published clinical trial : *Mascia et al. 2023 JAMA Oncology*

JAMA Oncology | Original Investigation

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases
The FAST-01 Nonrandomized Trial





Ongoing clinical trials :

FAST-02
Proton FLASH

IMPulse
Electron FLASH

LANCE
Electron FLASH

Upcoming clinical trials :

Electron FLASH

FLASH RT and IOERT

New technology : reduces toxicity while maintaining anti-tumour efficacy

A large volume of preclinical data has been published on electrons

Highly effective in a single high-dose fraction

Deliverable by mobile linear accelerators

Treatment time less than one second

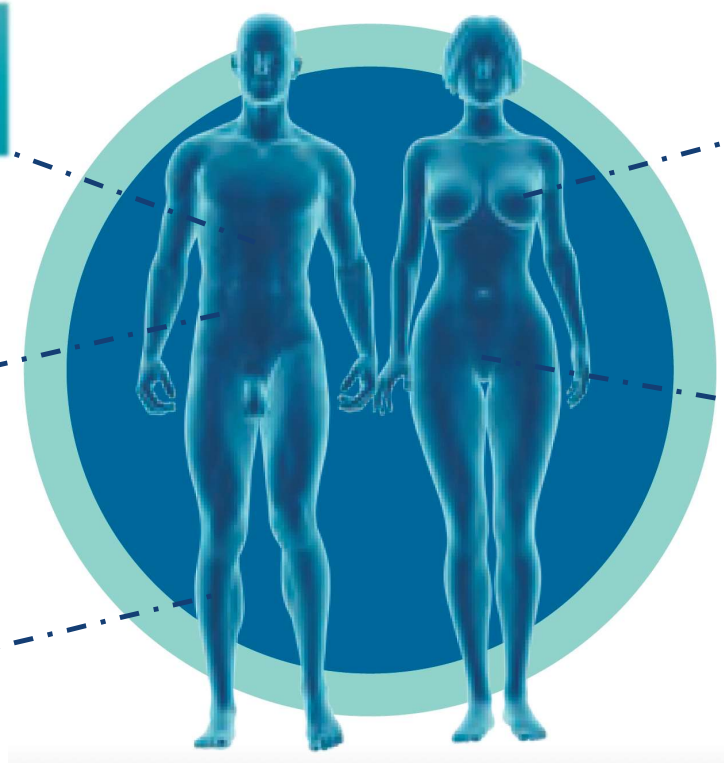
A PERFECT MATCH WITH THE IOERT ?

FLASH RT and IOERT

Pancreatic Cancer
Borderline resected
Locally advanced unresected

Soft tissue Sarcoma
Retroperitoneal

Soft tissue sarcoma
Extremity



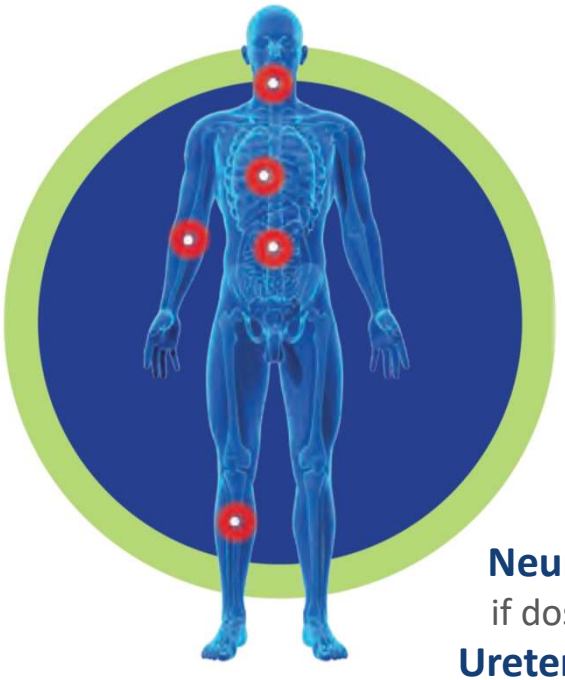
Breast Cancer
Exclusive
Boost

Rectal Cancer
Locally advanced
Locally recurrent

ESTRO IORT Task Force/ACROP

NCCN National Comprehensive Cancer Network®

FLASH RT and IOERT : Soft Tissue Sarcoma (STS)



Extremity STS : IOERT as a Boost
Retroperitoneal STS : IOERT as a Boost

Doses :

Suspected close margins : 10-12.5Gy
Suspected involved margins R1 : 12-15Gy
Gross residual disease R2 : 20 Gy

Potential benefits of Flash-IORT ?

Reducing toxicities :

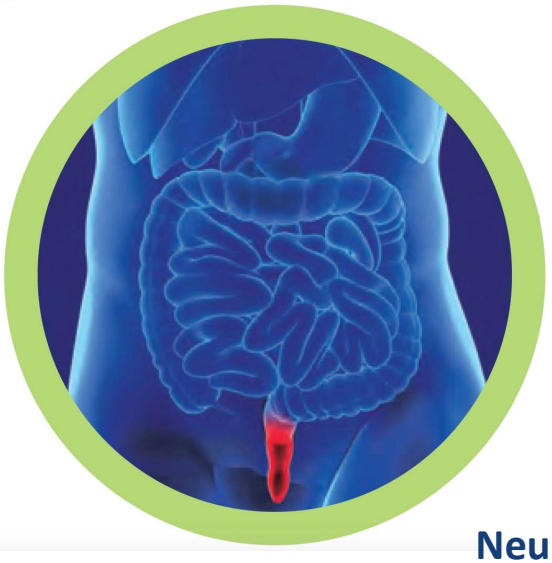
Neuropathy : risk of (severe neuropathy) seems to increase extensively if doses of >12.5 Gy are applied ***Haddock et Al. 2011***

Ureteral stenosis : frequently described in association with IORT in the retroperitoneal space ***Miller et Al. 2006***

Improve functionnal outcome : Impact of muscles fibrosis ?

Dose-escalation Role ? Large volume lesions >250cc ?

FLASH RT and IOERT : Rectal cancer



Locally recurrent rectal cancer : As Boost
Locally advanced rectal cancer : As boost

Doses :

Locally recurrent rectal cancer :
- **R0-R1 : 10-12.5Gy**
- **R2 : 15-20 Gy**

Locally advanced rectal cancer :
- **RO : 10–12.5 Gy**
- **R1 : 12.5–15 Gy**
- **R2 : 17.5–20 Gy**

Potential benefits of Flash-IORT ?

Reducing toxicities :

Neuropathy : IOERT doses of 12.5 Gy or less 5% incidence of grade 2–3 compared to 14% for IORT doses of 15 Gy or higher ***Hyngstrom et al. 2014***

Ureteral stenosis : Ureter dysfunction : 56% of ureters included in the IOERT field (any dose) and in less than 15% of ureters excluded ***Gunderson et al. 1997***

Ultra-fast beam delivery : Avoids the accumulation of fluids

Dose-escalation Role ? Benefits for R2 margins?

FLASH RT and IOERT : Pancreatic cancer

Borderline resected pancreatic cancer : as boost
Locally advanced pancreatic cancer unresected : as boost

Doses :

Borderline resected :
R0 : 10-12.5 Gy
R1 : 12.5-15Gy
R2 : 15-20 Gy

Locally advanced unresected :
R2 : 15–20 Gy

Potential benefits of Flash-IORT ?

Reducing toxicities ?

Duodenum, Major vessels, Spinal cord

Ultra-fast beam delivery : Avoids the accumulation of fluids

Dose-escalation Role : Highly resistant to radiation therapy ablative doses exceeding 70 Gy are needed for effective tumor control.

Post SBRT Neo-adjuvant RT ?

FLASH RT and IOERT : Breast cancer

All breast cancers requiring a boost : as boost
Eligibility criteria according APBI guidelines : Exclusive single dose

Doses :

Exclusive :	**As boost :**
21 Gy	**9-12 Gy**

Potential benefits of Flash-IORT for boost candidates ?

Dose-escalation Role ? :

Local control with IORT boost is already optimal : 98,4 % 10y F-U ! ***Fastner et al.***
DCIS ? Young patient <40y ? NACT non-responder ?

Reducing toxicities ? :

Cosmetic results are in favour of IORT , preclinical results in subcutaneous tissue suggest a reduction in adherences ***Vozenin et al. 2019***
Benefit in ultra-hypo fractionated schemes ?

FLASH RT and IOERT : Breast cancer

Potential benefits of flash for exclusives candidates ?

Dose-escalation Role ? :

Local control is the most frequent objection to exclusive IORT in breast cancer
But is the dose the problem ? Or the volume covered ?

Reducing toxicities ? :

Toxicity in exclusive IORT is low, but according to preclinical data we can expect a 30% reduction in scar fibrosis ***Vozenin et al. 2019***

Increase in irradiated volume ? :

FLASH IOERT could cover the tumour bed with wider margins at doses of 21 Gy
The skin would no longer be a problem in terms of toxicity ?
Applicator placed directly on the skin, without enlarging the scar

FLASH RT and IOERT : Conclusions

Although strong evidence has been demonstrated in pre-clinical trials the mechanisms producing the FLASH effect are still unclear

Current and future clinical trials in humans will pave the way for a multitude of clinical studies targeting different pathologies

Flash radiotherapy seems to have all the attributes needed for clinical translation in intraoperative electron radiotherapy

The clinical trials currently ongoing in IORT will make it possible to define where FLASH radiotherapy could provide the greatest benefit

Current developments in systemic therapies will undoubtedly open up new perspectives. The role of IORT and FLASH radiotherapy will need to be taken into account in the evolving management of cancer

Thank you

ANY QUESTIONS ?