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Exploring the Potential of Pulsed Dose Rate Brachytherapy: Radiobiological Foundations and Clinical Implications in Locally Advanced Cervical Cancer

Pierre Annède

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Pierre Annède. Exploring the Potential of Pulsed Dose Rate Brachytherapy: Radiobiological Foundations and Clinical Implications in Locally Advanced Cervical Cancer. Cellular Biology. Université Paris-Saclay, 2023. English. NNT : 2023UPASL054 . tel-04272319

HAL Id: tel-04272319

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Exploring the Potential of Pulsed Dose Rate Brachytherapy: Radiobiological Foundations and Clinical Implications in Locally Advanced Cervical Cancer

*Explorer le Potentiel de la Curiethérapie à Débit de Dose
Pulsé : Fondements Radiobiologiques et Implications
Cliniques dans le Cancer du Col Utérin Localement Avancé*

Thèse de doctorat de l'université Paris-Saclay

École doctorale n°582 : cancérologie : biologie - médecine - santé (CBMS)
Spécialité de doctorat : Sciences de la vie et de la santé
Réfèrent : Faculté de médecine

Thèse préparée dans l'unité de recherche : Radiothérapie Moléculaire et Innovation
Thérapeutique (Université Paris-Saclay, Institut Gustave Roussy, Inserm), sous la direction
de **Cyrus CHARGARI**, Professeur des universités, et sous la co-direction de **Charlotte
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Acknowledgments

Au professeur Philippe Maingon,

Je tiens à vous remercier d'avoir dirigé la soutenance d'une main de maître. Votre expertise dans cet exercice nous a permis à tous de profiter pleinement de cet événement très particulier. Votre dévouement dans le domaine de l'enseignement est exemplaire, et je vous exprime ma gratitude au nom de tous vos étudiants et disciples que vous avez formés.

Dear Professor Kari Tanderup,

I am truly grateful for the privilege of having you as a member of the jury for my thesis. Your presence has been an immense honor. I would like to extend my heartfelt appreciation for your unwavering availability and the invaluable insights, remarks, and constructive feedback you shared during the review of my manuscript and the defense. I eagerly anticipate following your future publications in the field.

Au professeur Christophe Hennequin,

Je tiens à vous exprimer ma sincère gratitude pour votre disponibilité sans faille et d'avoir accepté d'évaluer ce travail avec attention. Votre expertise dans le domaine de la radiobiologie est inestimable et a grandement contribué à la qualité de cette thèse.

Dear Professor Bradley Pieters,

I would like to express my gratitude for accepting to be present and evaluate this work. As always, you are full of insightful ideas, and your expertise in this field is remarkable. It is always a great pleasure to work with you, and I hope we can continue our collaborations in the future.

À Charlotte Robert,

Merci de m'avoir guidé dans les méandres du monde universitaire. Ton dynamisme et ton rôle moteur dans la recherche à Gustave Roussy sont remarquables.

Au professeur Cyrus Chargari,

Merci pour ton soutien sans faille. Depuis le début tu es toujours présent. A Paris, Marseille ou Toulon, l'histoire ne s'arrête pas là, hâte de continuer à travailler ensemble ! Merci pour tout !

À mes amis et à ma famille,

Je souhaite exprimer ma profonde gratitude à tous pour votre soutien indéfectible et vos encouragements au cours de ces longues années. Je tiens particulièrement à remercier Jo, Cam et Ilo pour avoir toujours été mes premières supportrices. Votre présence et votre soutien ont été d'une importance capitale pour moi.

Abstract

The dose/rate effect has been the main focus of radiobiological research in brachytherapy treatments, while data on other influencing factors remain limited. Preclinical studies have established the theoretical radiobiological superiority of pulsed dose rate (PDR) and low-dose rate over high-dose rate brachytherapy, and biological and predictive models have been developed to set up optimal brachytherapy modalities for specific situations.

Despite the promise of PDR brachytherapy regarding preclinical studies, there is a noticeable lack of clinical evidence to support these findings. A meta-analysis of patients with anal canal cancer is presented, uncovering consistent insights into the potential clinical advantages of PDR. These benefits include the capacity to administer higher radiation doses and attain comparable levels of local control in locally advanced diseases, through dose escalation, as seen in more localized tumors, without increasing side effects.

Finally, the potential of PDR brachytherapy in improving local control in a fraction of locally advanced cervical cancer patients, without increasing the risk of side effects, is explored. Factors have been identified to determine which patients might benefit from PDR brachytherapy, and insights on how to advance in this area are discussed.

Resumé

L'impact du débit de dose a été le principal axe de recherche en radiobiologie pour les traitements par curiethérapie, tandis que les données sur d'autres facteurs d'influence restent limitées. Les études précliniques ont établi la supériorité radiobiologique théorique de la curiethérapie à débit de dose pulsé (PDR) et bas débit de dose par rapport au haut débit de dose, et des modèles biologiques et prédictifs ont été développés pour aider à déterminer les modalités de curiethérapie optimales pour des situations spécifiques.

Malgré les promesses de la curiethérapie PDR sous tendues par les données précliniques, il existe un manque notable de preuves cliniques pour étayer ces résultats. Une méta-analyse sur des patients atteints de cancer du canal anal est présentée, révélant des informations concordantes sur les avantages cliniques potentiels de la curiethérapie PDR. Cela inclut la possibilité de délivrer des doses élevées et d'obtenir, grâce à l'escalade de dose sur des maladies localement avancées, des niveaux de contrôle local similaires à ceux des tumeurs plus localisées, sans augmentation des effets secondaires.

Enfin, le potentiel de la curiethérapie PDR pour améliorer le contrôle local dans une fraction de patients atteints de cancer du col utérin à un stade localement avancé, sans augmenter le risque d'effets secondaires, est exploré. Des facteurs ont été identifiés pour déterminer quels patients pourraient en bénéficier. Ces résultats permettent également d'évaluer les futurs axes de recherche à privilégier.

Scientific Publications Related to the Thesis

Directly related to this thesis

Annede P, Dumas I, Schernberg A, Tailleur A, Fumagalli I, Bockel S, et al. Radiobiological optimization comparison between pulse-dose-rate and high-dose-rate brachytherapy in patients with locally advanced cervical cancer. *Brachytherapy*. 2019 Jun;18(3):370–7.

Annede P, Cosset J-M, Van Limbergen E, Deutsch E, Haie-Meder C, Chargari C. Radiobiology: Foundation and New Insights in Modeling Brachytherapy Effects. *Semin Radiat Oncol*. 2020;30(1):4–15.

Annede P, Ferre M, Kirisits C, Pieters BR, Schmid M, Strnad V, et al. Brachytherapy boost in anal canal cancer - A GEC ESTRO PDR task force meta-analysis. *Clin Transl Radiat Oncol*. 2023 Mar;39:100589.

Annede P, Robert C, Espenel S, Dumas I, Chargari C. Redefining the Role of Pulsed-Dose-Rate Brachytherapy in Cervical Cancer Treatment using a Pre-Planned Approach. *Submitted*.

Indirectly related to this thesis

Ferré M, Varela Cagetti L, Zemmour C, Tyran M, Fau P, Chargari C, Tallet A, Gonzague L, **Annede P**. Reducing dose to rectum by placement of a rectum-emptying tube in cervical cancer patients treated with brachytherapy. *Brachytherapy*. 2021 Jul-Aug;20(4):748-754.

Schernberg A, Bockel S, **Annede P**, Fumagalli I, Escande A, Mignot F, et al. Tumor Shrinkage During Chemoradiation in Locally Advanced Cervical Cancer Patients: Prognostic Significance, and Impact for Image-Guided Adaptive Brachytherapy. *Int J Radiat Oncol Biol Phys*. 2018 01;102(2):362–72.

Kissel M, Chirat E, **Annede P**, Burtin P, Fumagalli I, Bronsart E, Mignot F, Schernberg A, Dumas I, Haie-Meder C, Chargari C. Esophageal brachytherapy: Institut Gustave Roussy's experience. *Brachytherapy*. 2020 Jul-Aug;19(4):499-509. doi: 10.1016/j.brachy.2020.04.002. Epub 2020 May 20.

Schernberg A, Kumar T, Achkar S, Espenel S, Bockel S, Majer M, Escande A, Mignot F, **Annede P**, Monnier L, Huguet F, Chargari C. Incorporating Magnetic Resonance Imaging (MRI) Based Radiation Therapy Response Prediction into Clinical Practice for Locally Advanced Cervical Cancer Patients. *Semin Radiat Oncol*. 2020 Oct;30(4):291-299.

Mignot F, Gouy S, Schernberg A, Bockel S, Espenel S, Maulard A, **Annede P** et al. Comprehensive analysis of patient outcome after local recurrence of locally advanced cervical cancer treated with concomitant chemoradiation and image-guided adaptive brachytherapy. *Gynecol Oncol*. 2020 Mar 13;

Annede P, Gouy S, Haie-Meder C, Morice P, Chargari C. [Place of radiotherapy and surgery in the treatment of cervical cancer patients]. *Cancer Radiother*. 2019 Oct;23(6-7):737-44.

Annede P, Mailleux H, Sfumato P, Ferré M, Autret A, Varela Cagetti L, et al. Multivariate normal tissue complication probability modeling of vaginal late toxicity after brachytherapy for cervical cancer. *Brachytherapy*. 2018 Dec;17(6):922-8.

List of abbreviations

α/β ratio : alpha/beta ratio

BER : base excision repair

CI : confidence interval

CTV_{HR} : high-risk clinical target volume

CTV_{IR} : intermediate-risk clinical target volume

D2cc : minimal doses to the most exposed 2cc

D₉₀ CTV_{HR} : minimal dose to 90% of the high-risk clinical target volume (D₉₀ CTV_{HR})

D₉₈ CTV_{IR} : minimal dose to 98% of the intermediate-risk clinical target volume

DNA : deoxyribonucleic acid

EBRT : external beam radiation therapy

EQD2 : equivalent 2 Gy dose fractions

ESMO : European Society of Medical Oncology

FIGO : Fédération Internationale de Gynecologie et d'Obstetrique

GEC ESTRO : Groupe Europeen de CurietherapieEuropean Society for
Radiotherapy & Oncology

Gy : gray

HDR : high-dose rate

HT : hyperthermia

HR : homologous recombination

IDR : intermediate-dose rate

IMRT : intensity-modulated radiation therapy

IQR : interquartile range

LACC : locally advanced cervical cancer

LDR : low-dose rate

LET : low-linear energy transfer

LNCaP : Lymph Node Carcinoma of the Prostate

MRI : magnetic resonance imaging

NER : nucleotide excision repair

NHEJ : non-homologous end joining

OAR : organs at risk

PDR : pulsed-dose rate

pO₂ : partial pressure of oxygen

PRISMA : Preferred Reporting Items for Systematic Reviews and meta-analysis

RBE : relative biological effectiveness

ROS : reactive oxygen species

SD : standard deviation

T_{1/2} : halftime of tissue repair

TCD₅₀ : radiation dose required to control 50% of the tumor

TME : tumor microenvironment

UICC : Union for International Cancer Control

VLDR : very low-dose rate

Table of contents

Acknowledgments	1
Abstract	3
Scientific Publications Related to the Thesis	6
List of abbreviations	9
Table of contents	11
Tables and Figures	14
Introduction	17
1 State of the art in brachytherapy radiobiology	20
1.1 Background.....	20
1.2 Key Details in Brachytherapy Radiobiology.....	22
1.2.1 Historical Background and Definitions.....	22
1.2.2 DNA Repair.....	24
1.2.3 Cell Death and Cell Cycle Redistribution.....	28
1.2.4 Microenvironment.....	33
1.2.5 Repopulation.....	37
1.3 Practical Applications.....	39
1.3.1 LDR vs HDR vs PDR.....	39
1.3.2 Radiobiology Modeling.....	40
1.3.3 Dose Rate and Fractionation Optimization.....	43
1.3.4 Pharmacomodulation.....	48
Chemotherapy.....	49
Immunotherapy.....	50
Androgen Deprivation Therapy.....	51
Theranostics.....	52
Hyperthermia.....	52
1.4 Summary and outlook.....	54
2 PDR Brachytherapy: Does Clinical Evidence Support Radiobiological Models?	56
2.1 Background.....	56
2.2 Brachytherapy boost in anal canal cancer – A GEC ESTRO PDR task force meta-analysis.....	57
2.2.1 ABSTRACT.....	58
2.2.2 Introduction.....	59
	11

2.2.3 Materials and methods.....	60
Protocol.....	60
Study selection.....	60
Outcomes.....	63
Clinical & treatment data.....	63
Data synthesis and analysis.....	63
2.2.4 Results.....	64
Patient and tumor characteristics.....	64
Treatment characteristics.....	64
Survival outcomes.....	67
Toxicities.....	68
2.2.5 Discussion.....	69
2.2.6 Conclusion.....	72
2.3 Summary and outlook.....	73
3 Exploring the theoretical potential of PDR in LACC patients.....	74
3.1 Background.....	76
3.1 Radiobiological optimization comparison between pulse-dose-rate and high-dose-rate brachytherapy in patients with locally advanced cervical cancer..	78
3.1.1 ABSTRACT.....	79
3.1.2 Introduction.....	81
3.1.3 Methods.....	83
Patient population.....	83
Linear quadratic model.....	83
PDR brachytherapy procedure.....	83
Conversion to HDR planning treatment.....	84
Data extraction and statistics.....	84
3.1.4 Results.....	86
Patients and EBRT dose contribution.....	86
Pulse-dose rate brachytherapy.....	86
High-dose rate brachytherapy.....	87
Linear-quadratic model effect.....	87
Radiobiological optimization.....	90
3.1.5 Discussion.....	92
3.1.6 Conclusion.....	95
3.2 Redefining the Role of Pulsed-Dose-Rate Brachytherapy in Cervical Cancer Treatment using a Pre-Planned Approach.....	96
3.2.1 Abstract.....	97

3.2.2 Introduction.....	98
3.2.3 Methods.....	99
Data.....	99
Dosimetry process.....	99
Data extraction and endpoints:.....	100
Selection of the best experimental brachytherapy modality:.....	100
Determination of the group of high risk patients benefiting the most from the PDR modality:.....	100
Sensitivity analysis.....	100
Statistical analysis:.....	101
3.2.4 Results.....	102
Patient and tumors characteristics:.....	102
Dosimetric results:.....	102
Selection of the best experimental brachytherapy modality:.....	102
Selection of the group of high-risk patients most likely to benefit from PDR:..	103
Best experimental arm versus the control arm:.....	103
Sensitivity analysis.....	108
Feasibility of a randomized clinical trial:.....	109
3.2.5 Discussion.....	113
Conclusion.....	117
References.....	119
Appendix.....	135
Long résumé en Français.....	141

Tables and Figures

Figures

Figure 1.1. The six main features of radiobiology.....	21
Figure 1.2. Brachytherapy categories according to dose rate.....	23
Figure 1.3. Incomplete repair principle.....	24
Figure 1.4 : Dose response curves for Chinese hamster cells (CHL-F line) grown in vitro and exposed to ⁶⁰ Co gamma-rays at various dose-rates.....	25
Figure 1.5. Sparing effect of low-dose rate brachytherapy to healthy tissue following their repair half-time.....	26
Figure 1.6. Biological effective dose (BED) ratio for pulsed-dose rate (PDR) to the effect of continuous low-dose rate (LDR).....	28
Figure 1.7. Effect of radiation to the cell cycle, overview of the checkpoints.....	29
Figure 1.8. Fraction of Chinese hamster cells surviving a dose for 660 rads and 1000 rads, function of age at radiation exposure.....	30
Figure 1.9. Dose-response ratios - acute to continuous irradiation function of the dose rate.....	32
Figure 1.10. schematic representation of dose heterogeneity of brachytherapy delivery and its subsequent impact on the tumor microenvironment.....	35
Figure 1.11. Illustration of the oxygen effect.....	36
Figure 1.12. Biphasic repair concept.....	42
Figure 1.13 EQD2 to the tumor as the function of EQD2 to the OAR according to the linear quadratic model.....	46
Figure 1.14. Comparison of EQD2 to OAR between HDR and PDR brachytherapy in locally advanced cervical tumor patients.....	48
Figure 2.1. PRISMA flow diagram illustrating the systematic process conducted to select data.....	61
Figure 2.2. Forest plot of five-year local recurrence-free survival rate.....	67

Figure 2.3. Forest plot of the proportion of colostomy related to toxicity.....	68
Figure 3.1.1. Paired box plot of target and normal tissue metrics following brachytherapy modality.....	88
Figure 3.1.2. Linear-quadratic model for organs at risk (α/β ratio) and target volumes (α/β ratio = 10Gy).....	89
Figure 3.1.3. Comparison of 2 Gy equivalent dose (EQD2) between high-dose-rate and pulse-dose-rate brachytherapy.....	90
Figure 3.1.4. Therapeutic ratio of HDR relative to PDR, according to total number of hourly pulses.....	91
Figure 3.2.1. Boxplot of the metrics.....	104
Figure 3.2.2. Histogram of patients reaching the target clinical goal for D90 CTVHR...	105
Figure 3.2.3. Correlation Matrix between TCP Increase and several variables.....	107
Figure 3.2.4. Principal Component Analysis.....	108
Figure 3.2.5. Alternative D90 CTVHR EQD2 and TCP estimation calculated using other values of α/β ratio and T1/2.....	110
Figure 3.2.6. Alternative D2cc bladder EQD2 calculated using other values of T1/2 (A) and α/β ratio (B).....	111
Figure 3.2.7. D2cc bladder EQD2 function of D90 CTVHR EQD2.....	112

Tables

Table 2.1. Patient and tumor characteristics.....	62
Table 2.2. Alternative EQD2 estimation.....	65
Table 2.3. Treatment characteristics.....	66
Table 3.1.1. Dosimetry of targets volume and organs at risk.....	87
Table 3.2.1. Metrics and Tumor Control Probability.....	106

Appendix

Appendix 1. R script chunk developed for extracting brachytherapy dosimetric data from ".dvh" files.....	135
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Appendix 2. R script chunk developed for converting brachytherapy physical dose to EQD2.....	137
Appendix 3. R script chunk developed to set TCP model from Tanderup et al.,2016....	139
Appendix 4. R script chunk developed for sample size estimation from survival time published by Tanderup et al., 2016.....	140

Introduction

Cervical cancer is a significant public health issue, particularly in developing countries where it is one of the leading causes of cancer-related deaths among women. The current standard of care for locally advanced cervical cancer involves a combination of chemotherapy and external beam radiation therapy (EBRT) followed by brachytherapy, a form of internal radiation therapy that involves the placement of radioactive sources within or in close proximity to the tumor. Brachytherapy has been shown to provide several advantages over EBRT, including a more conformal dose distribution, a shorter treatment time, and a higher therapeutic ratio. It is also associated with fewer side effects and complications compared to EBRT, and is considered a standard of care.(1)

There are several competing technologies in brachytherapy, including high-dose rate (HDR), pulsed-dose rate (PDR), low-dose rate (LDR), and very low-dose rate (VLDR) brachytherapy, each with its own radiobiological characteristics and logistical issues. While HDR is by far the most widely used modality, PDR is still preferred for treating sensitive areas such as the anal canal, penile glans, vagina, oral mucosa, reirradiation, and particularly for the treatment of pediatric cancers.(2–7) However, the logistical and economic considerations of PDR limit its use in many centers, and there is a risk that there will be too few LDR and PDR users left, leading to the industry shutting down production focusing on HDR.(8,9)

Despite the potential benefits of PDR, its superiority over HDR has never been properly assessed in a sufficiently powered randomized clinical trial. Even retrospective data comparing the two modalities are scarce. The main rationale for using PDR instead of HDR is based on radiological data mostly obtained from preclinical studies and mathematical models. In daily practice, the equivalent dose between PDR and HDR is estimated using the linear quadratic model. Following this model, PDR allows for the possibility of escalating dose to the target and/or limiting the exposure of organs at risk, improving the therapeutic window.(10) However, as far as we know, in the setting of cervical cancer treated by modern brachytherapy with dose escalation through magnetic resonance imaging-based adaptive

techniques and interstitial implantation, the theoretical benefit of PDR over HDR has never been properly estimated.

The aim of this thesis is to assess the potential of PDR brachytherapy for locally advanced cervical cancer in the modern era. To achieve this goal, three steps were taken.

1. We performed a thorough review of the knowledge in the field of brachytherapy radiobiology.

2. To obtain clinical evidence that PDR could yield better outcomes and to see if radiological knowledge is corroborated by clinical evidence, we conducted a meta-analysis comparing clinical outcomes of PDR vs HDR in anal canal cancer patients. The anal canal was selected because we estimated that it was the location with the highest chance of reaching significance.

3. Based on the linear quadratic model, tumor control probability (TCP) model extracted from a large cohort and dosimetric data of locally advanced cervical cancer patients, we estimated the proportion of patients that could benefit from PDR over HDR and assessed the theoretical clinical impact expected.

1 State of the art in brachytherapy radiobiology

1.1 Background

Brachytherapy has been used as a component of care for gynecologic, prostate, breast, pediatric, head and neck, and other cancers.(11–13) It is characterized by heterogeneous dose distributions with sharp dose gradients following the inverse square law and absorption, and remains an unmatched treatment modality allowing for the delivery of high doses to the indicated target volume(s) while sparing organs at risk (OAR). The sharp dose gradients result in the delivery of a large range of doses and dose rates to the target volume, which complicates the understanding of the radiobiological effects. Limited data are available regarding the opportunities for radiobiological optimization.

On the contrary, there have been a number of technological developments that have allowed for improvements in dosimetric optimization for brachytherapy. One improvement is the capability to anticipate the placement of applicators and needles. Fokdal et al. investigated the use of virtual preplanning using magnetic resonance imaging images acquired with intracavitary/interstitial hybrid applicators in situ approximately 1 week prior to brachytherapy to investigate whether interstitial needles were necessary to improve the dosimetric coverage of the target volume(s) and minimize dose to the OARs.(14)

However, it is unclear how the dose rate effect could be used as a tool to increase the therapeutic index. Examining the expected contribution of brachytherapy to target volume coverage and OARs dose might potentially be used to guide physicians in determining which brachytherapy modality (PDR or HDR) would be the most appropriate given the specific clinical situation. Early dosimetric studies suggest that radiobiological optimization based on dose rate modification may be useful in certain situations.(15) However, these strategies rely on a good understanding of the radiobiological phenomena in order to estimate the therapeutic index according to the available brachytherapy modalities.

Several factors will impact tissue response to brachytherapy such as OAR and tumor radiosensitivity, dose rate for protracted LDR brachytherapy, pulse size for

PDR brachytherapy, and fractionation for HDR brachytherapy. In addition to the “4R” concept (ie, DNA [Deoxyribonucleic acid] repair, reoxygenation, cell cycle redistribution, and repopulation) of radiobiology, other biological mechanisms will also play a role in tissue response including interactions within the cellular microenvironment and the potential effects of immune response. These six main features of radiobiology are illustrated in **Figure 1.1**. (16,17) To utilize brachytherapy to its fullest potential requires time and experience, as well as a good understanding of radiobiology.

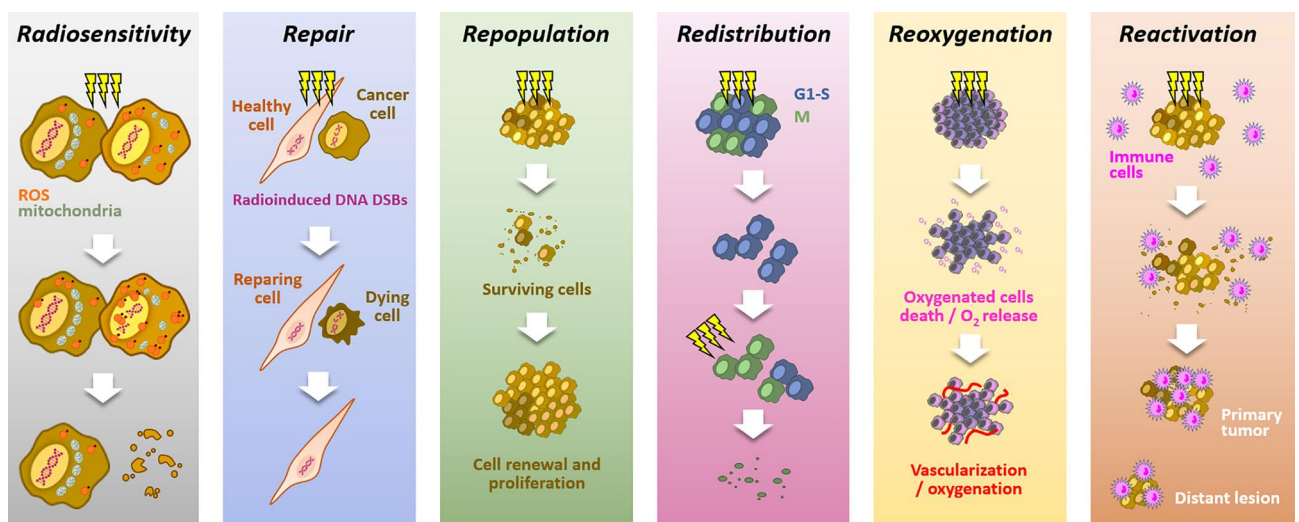


Figure 1.1. The six main features of radiobiology. From Rakotomalala et al., 2021.(17) This illustration describes the six main parameters of radiobiology that impact the response to radiotherapy: radiosensitivity, repair, repopulation, redistribution, reoxygenation, and reactivation. These parameters influence cell responses to irradiation, the capacity of cells to repair radio-induced damages, tumor growth following radiotherapy, progression of cancer cells, oxygen level recovery, and immune response triggered by irradiation-induced immunogenic cell deaths.

1.2 Key Details in Brachytherapy Radiobiology

1.2.1 Historical Background and Definitions

LDR brachytherapy was the original modality used to deliver brachytherapy treatments. In the absence of technology that allowed for quick and efficient calculations of treatment plans, implant systems that detailed specific rules regarding the distribution of sources were developed to allow for reproducible implants and doses from these implants (e.g. Manchester system, Stockholm system, Paris system). Initially, temporary brachytherapy applications were delivered with ^{226}Ra , which was later replaced with radioisotopes such as ^{137}Cs for intracavitary applications and ^{192}Ir wires for interstitial implants. In the early 1960s, remote afterloading technology was introduced which allowed sources such as ^{192}Ir and to a lesser extent ^{60}Co and ^{137}Cs , to be introduced after the placement of a brachytherapy applicator and with the patient treated in a shielded vault using a control system that can extend, move, and retract the source.(18)

Brachytherapy can be divided into 4 categories according to dose rate, shown in **Figure 1.2.**(19)

- 1) HDR brachytherapy is defined by the International Commission on Radiation Units and Measurements as a source that delivers a dose rate greater than 12 Gy/h at a point or surface where the dose is prescribed, and is primarily used in the treatment of cervical, vaginal cuff, prostate, breast, esophagus and bronchus cancers.(20)
- 2) Intermediate dose rate brachytherapy (IDR), that is defined by a dose rate ranging from 1 to 12 Gy/h and is used for the treatment of cervical and breast tumors.
- 3) Continuous LDR brachytherapy, that encompasses dose rates ranging from 0.4 to 1 Gy/h and is used to treat cervical cancer and locations at high risk of complication (eg, vulva, vagina, head and neck mucosa, anal canal, penile glans, and pediatrics cancer). It should be highlighted that historically, the definition of LDR was limited to a maximum dose

rate of 2 Gy/h. Due to clinically relevant differences at dose rates >1 Gy/h, this definition was refined to a maximum dose rate of 1 Gy/h.(20)

- 4) VLDR brachytherapy, that is defined by dose rates less than 0.4 Gy/h (usually <1 Gy/day) and is commonly used in permanent implants involving ^{125}I or ^{103}Pd seeds to treat prostate cancers either, as monotherapy or as a boost to EBRT.(20)

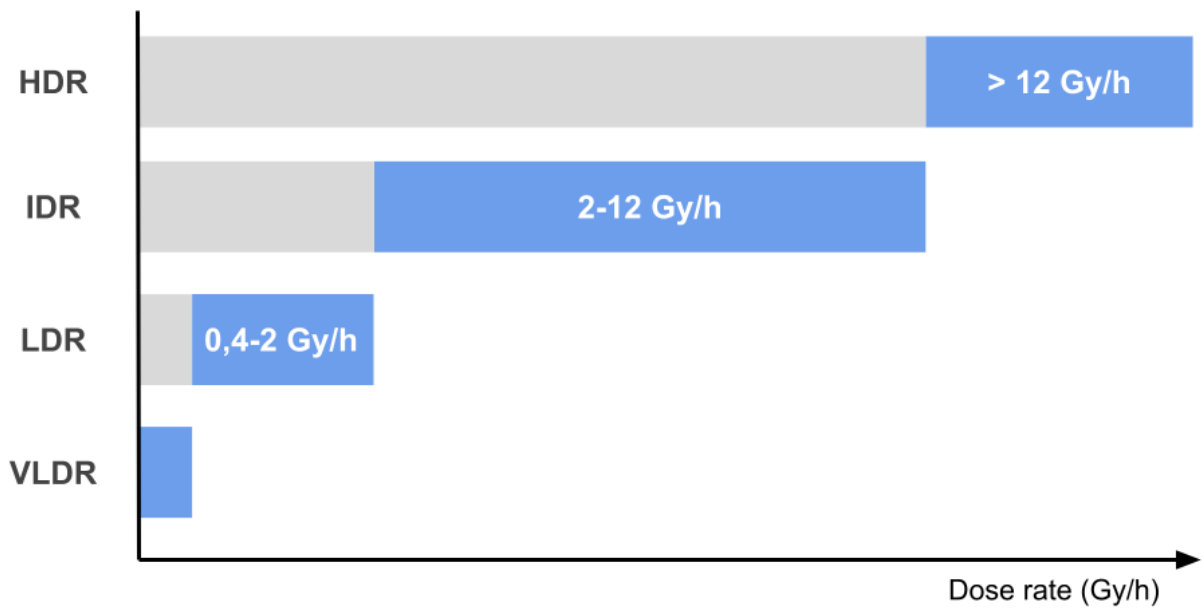


Figure 1.2. Brachytherapy categories according to dose rate.

HDR : high-dose rate, IDR : intermediate-dose rate, LDR : low-dose rate, VLDR : very low-dose rate

Although not a separate dose rate category, PDR brachytherapy is another brachytherapy modality in use. PDR brachytherapy is hyperfractionated HDR delivered in hourly pulses that extend over several days. The repeated irradiation over the treatment course is believed to mimic the radiobiological effects of LDR brachytherapy, resulting in incomplete repair between the pulses. As such, some believe PDR brachytherapy offers the best of LDR and HDR brachytherapy, namely the radiobiological benefit of LDR with the radiation safety benefit due to remote delivery of HDR.

1.2.2 DNA Repair

Cell death following irradiation may be caused by lethal DNA damage which is irreversible and irreparable, potentially lethal damage which becomes lethal if not repaired, and sublethal damage which can become lethal if the cell is irradiated again within a given time frame before it can be repaired, resulting in a cumulative dose effect.(21) These phenomena, primarily observed in studies involving mammalian cells, have been modeled using the “incomplete-repair” formalism, illustrated in **Figure 1.3**.(22)

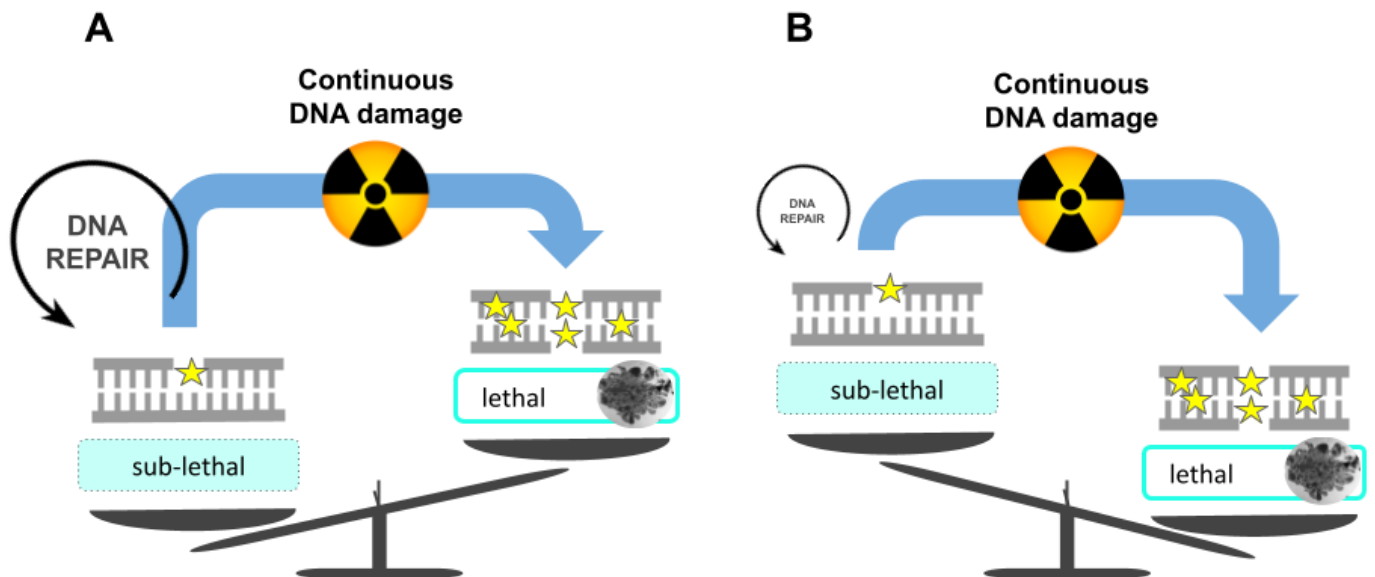


Figure 1.3. Incomplete repair principle. **A** : Typical slowly proliferating tissue with high DNA repair capability (low half time of repair), **B** : Typical tumor tissue with low DNA repair capability (high half time of repair)

For fractionated treatments with high doses per fraction (e.g. HDR brachytherapy), the capacity to repair sublethal and potentially lethal damage is dependent on fraction size, repair capacity (α/β value) and the time interval between fractions. On the contrary, for protracted treatments, as in the case of continuous low dose-rate irradiation such as LDR brachytherapy, potentially lethal damage repair can occur during treatment. In this case, dose rate, repair capacity, and half time of repair

are the determinant factors affecting radiation response. The enhancement of the dose-response relationship as a function of dose rate is depicted in **Figure 1.4**.

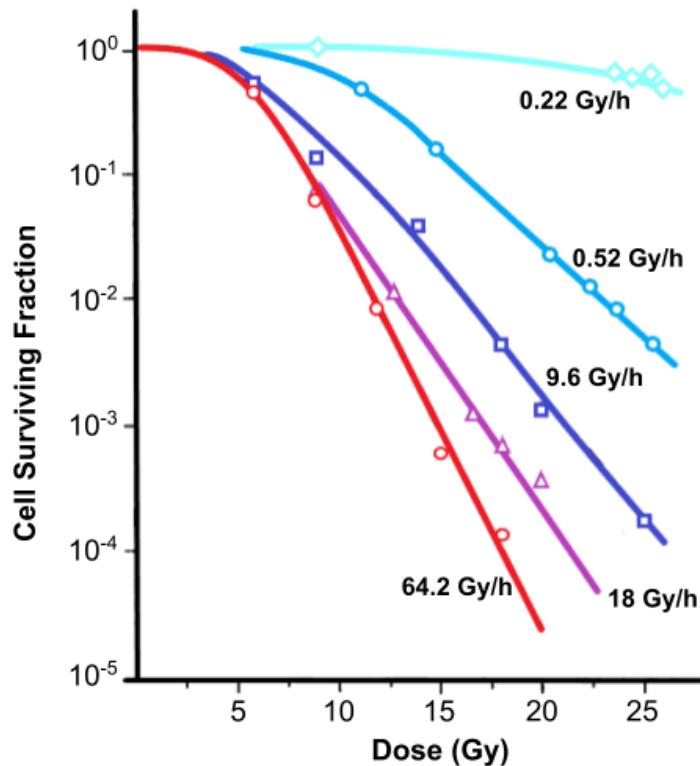


Figure 1.4. Dose response curves for Chinese hamster cells (CHL-F line) grown in vitro and exposed to ^{60}Co gamma-rays at various dose-rates. Derived from Bedford et al., 1973. (23,24)

The capacity to repair sublethal and potentially lethal damage plays a key role in differentiating the effects between tumor and OARs. In most situations, normal tissues are affected by late toxicities (slowly proliferating tissue), have a higher DNA repair capability (thus a lower half time of repair), and therefore, are more sensitive to dose per fraction or to dose rate than rapidly proliferating tumors with high half time of repair. In this scenario, LDR brachytherapy is theoretically superior to HDR brachytherapy due to its relatively improved OAR sparing potential, as illustrated in **Figure 1.5**.(23)

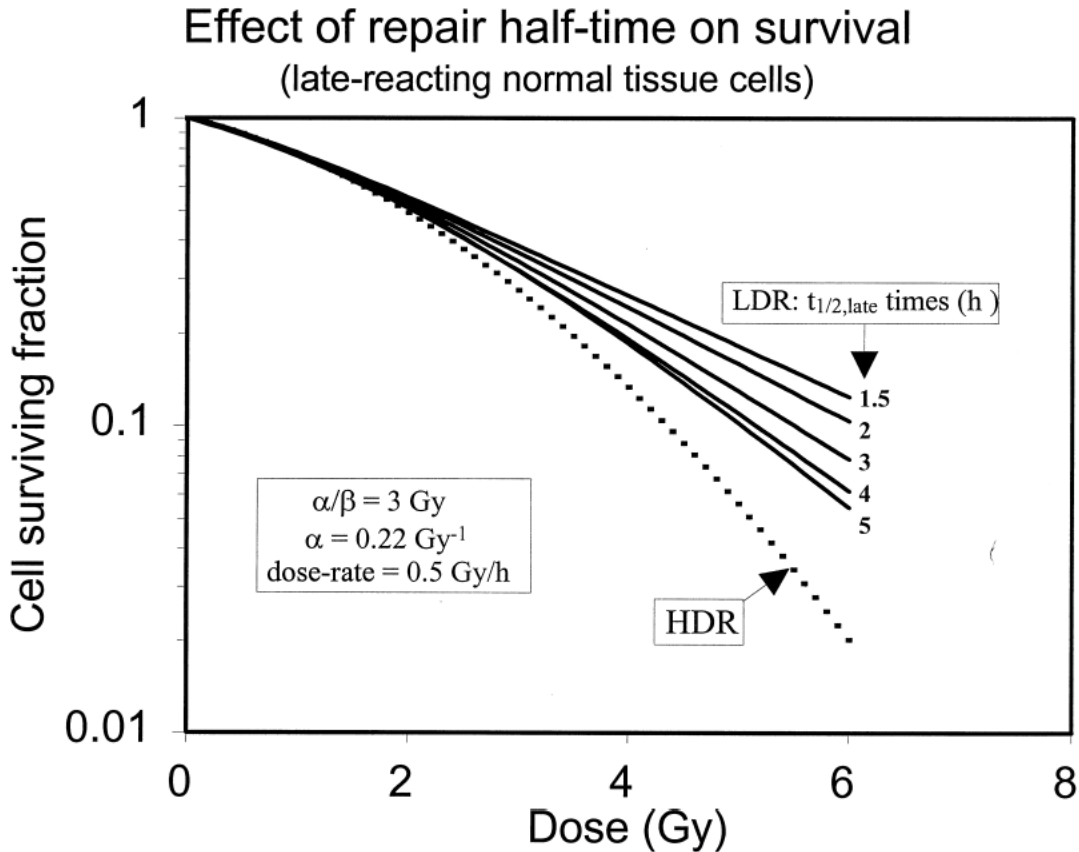


Figure 1.5. Sparring effect of low-dose rate brachytherapy to healthy tissue following their repair half-time. From Orton et al., 2001.(26) The effect of repair half-time ($t_{1/2}$) on cell survival for low-dose rate (LDR) radiation following the linear quadratic model is shown, along with its impact on the difference between LDR and high-dose-rate (HDR) radiation, which is not affected by repair half-time."

For LDR brachytherapy, the effect of dose rate on TCP and normal tissue complication probability has been well established. According to several clinical studies of gynecological or head and neck cancers, the optimal dose rate providing the best therapeutic index should be between 0.5 and 0.9 Gy/h.(25,27,28)

The radiobiological effects of permanent implants (eg, ^{125}I , ^{103}Pd), especially related to DNA repair, are difficult to interpret as the initial dose rate, the total dose, and the half-life of the radioisotope have to be taken into account. Over time, the dose rate for permanent implants will decay to levels that are so low that the implant no longer has a significant radiobiological effect.(29) However, for very low photon energies (eg, 28 keV for ^{125}I), the relative biological effectiveness (RBE) of permanent

implants is greater than other brachytherapy modalities. Preclinical studies have suggested an RBE of approximately 1.4 for ^{125}I at dose rates on the order of 0.07 Gy/h, and an RBE of 1.9 for ^{103}Pd .(30) Since permanent implants deliver their total dose over the course of several weeks, this may allow for tumor repopulation in rapidly proliferating tumors.

Several preclinical studies have suggested that PDR may be functionally equivalent to a temporary LDR implant when pulses are repeated every hour, the dose per pulse is less than 0.5-0.6 Gy/h, and the total dose and overall treatment time are unchanged.(31–35) In contrast to these theoretical considerations, preclinical studies have highlighted several significant differences between PDR and LDR brachytherapy in animal prostate tumor models. When prostate cancer tumors were transplanted to rats and treated with PDR brachytherapy (0.75 Gy/hour pulse size) or LDR (0.75 Gy/h), the tumor growth was found to be significantly lower in the PDR arm in total dose ranges of 20-30 Gy.(36) This difference in effect may be attributed to radiobiological factors that are sensitive to fractionation such as redistribution of cells over the cell cycle. Indeed, PDR brachytherapy, can be more toxic for cells than LDR because dose is delivered in a few minutes, with cell death resulting from single-event ($\alpha \cdot D$, linearly related to the dose) as well as multiple-event kills from unrepaired sublethal damage ($\beta \cdot D^2$, quadratically related to the dose). In the case of LDR, sublethal damage can be repaired. This differential effect is drastically impacted by the half time of repair and repetition time, as illustrated in **Figure 1.6.** (37)

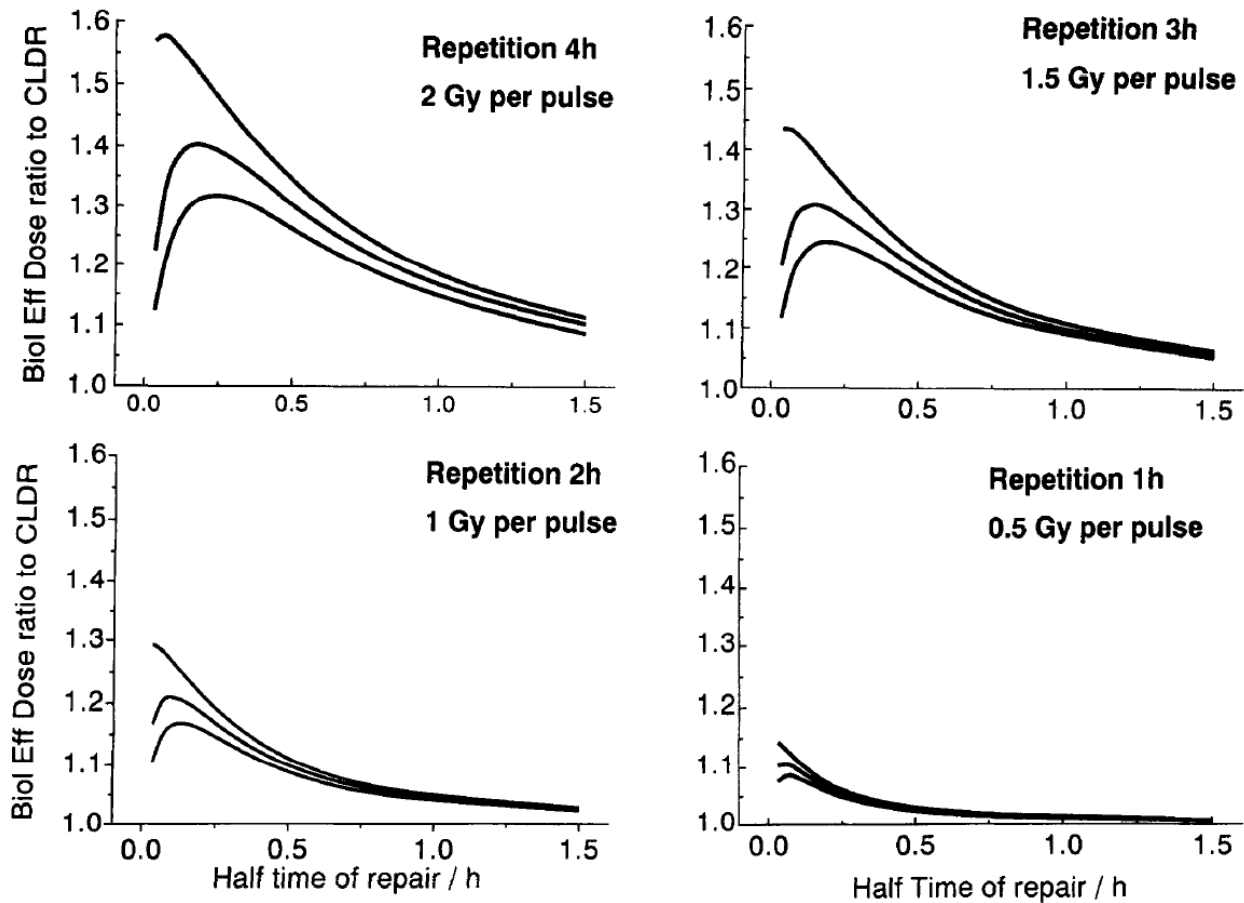


Figure 1.6. Biological effective dose (BED) ratio for pulsed-dose rate (PDR) to the effect of continuous low-dose rate (LDR). Fowler et al., 1997.(37) The curves depict the relationship between BED ratio and the half time of repair, plotted for three different average dose rates. The upper curve represents a dose rate of 120 Gy/h, the middle curve represents 10 Gy/h, and the lower curve represents 4 Gy/h. Considering a treatment of 70 Gy in an overall time of 140 h. These results are for late-responding tissues assuming $\alpha/\beta = 3$ Gy.

1.2.3 Cell Death and Cell Cycle Redistribution

Exposure of cells to ionizing radiation causes the cell cycle to arrest in the G1, S, or G2 phases. Cell arrest is associated with DNA repair processes before the cell is permitted to progress to the next phase or with cell death, in case of excessive damage.(38) Several mechanisms are involved in the coordinated response of DNA repair and activation of cell cycle checkpoints, including the tumor suppressor protein

p53 and inhibitors of DNA damage response such as ataxia-telangiectasia mutated kinase inhibitors.(39) While the G1/S checkpoint is p53 dependent, the G2/M checkpoint is regulated by multiple pathways. Therefore, cells with mutant p53 are more likely to undergo cell arrest in the G2/M phase, which is considered relatively radiosensitive, encouraging fractionation to exploit cell cycle redistribution.(40) Effect of radiation to the cell cycle is illustrated in **Figures 1.7. and 1.8.**

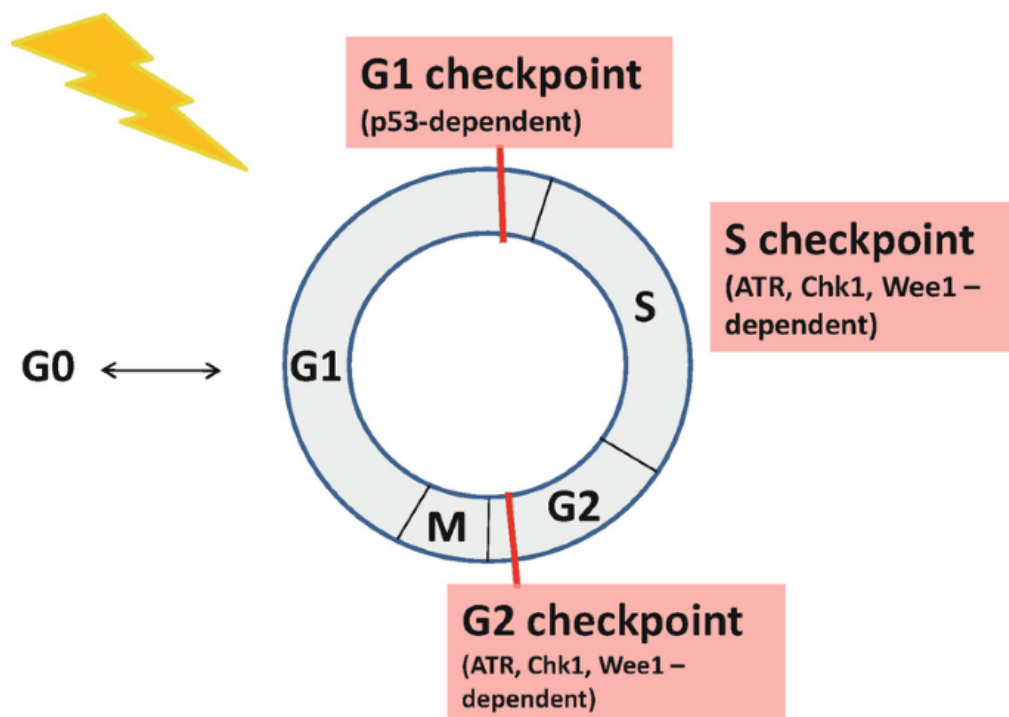


Figure 1.7. Effect of radiation to the cell cycle, overview of the checkpoints. From Syljuåsen, 2019. (41)

Indeed, the radiosensitivity of cells is dependent on their stage within the mitotic cycle. Radiation is more lethal in proliferating cells. Cells in the G2 and M phases of the cell cycle have been found to be approximately 3 times more radiosensitive than cells in the S phase. Although the exact mechanism for this phenomenon is uncertain, this could be explained in part by the activation of DNA repair during the S phase.(42)

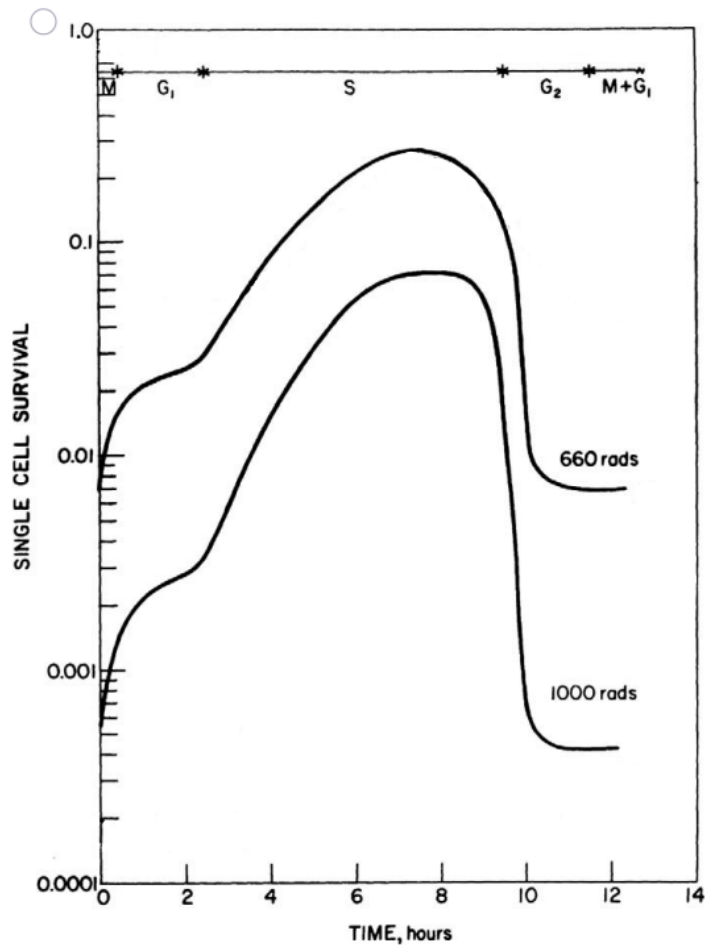


Figure 1.8. Fraction of Chinese hamster cells surviving a dose for 660 rads and 1000 rads, function of age at radiation exposure. Adapted from Sinclair et al., 2012. (43) At the top of the figure are the cell cycle phases corresponding to the age of the cells at the time of irradiation. 1Gy = 100 rads.

The radiobiological effects of LDR brachytherapy as it relates to the cell cycle have been investigated in human pancreatic cancer cell lines, using ^{125}I brachytherapy seeds which increased G2/M cell cycle arrest and apoptosis.(44) In gastric tumor xenografts, ^{125}I brachytherapy was reported to increase apoptosis within tumors, and was associated with G2/M cell arrest.(45) A study by Jian et al. also demonstrated that apoptosis was the main pathway to cell death when treating pancreatic carcinoma xenografts with ^{125}I brachytherapy seeds.(46)

While both PDR and LDR brachytherapy showed dose dependent effects on the cell cycle, PDR brachytherapy has been shown to be more effective in rat prostate tumor models. PDR brachytherapy resulted in a significantly greater

accumulation of cells in G2/M and a significant decrease of aneuploid cells in the G1-phase.(47)

In a study comparing the effects of single fraction HDR brachytherapy using ^{137}Cs (dose rate of 600 Gy/h) vs VLDR brachytherapy using ^{90}Y (dose-rate of 0.05-0.2 Gy/h) on lymphoma cells, a halt in G2/M and apoptosis was observed with both brachytherapy modalities. However, the cell line exposed to HDR was more sensitive.(48)

These results were corroborated in experiments on rat embryo cells transfected with oncogenes and irradiated using ^{60}Co brachytherapy with daily fractions of 5 Gy at different dose rates. It was observed in rat embryo cells transfected with c-myc oncogene that varying the dose rate from 3Gy/h to 60 Gy/h induced an increase in apoptotic fraction. At low doses, the rise was steep and reached 40% at 5 Gy. The apoptotic fraction plateaued to approximately 60% at doses >15 Gy. Cells transfected with ras oncogene were much less sensitive to dose rate in terms of apoptosis, with a maximum apoptotic rate of 10%. These data suggest that different sensitivities to the dose rate effect may be partially due to differences in susceptibility to apoptosis.(49)

Other in vitro studies have shown a decrease in proliferation rate and cell survival after brachytherapy in radioresistant human squamous cell carcinoma cell lines exposed to HDR brachytherapy, where an increased percentage of cells arrested in the G2/M phase. Contrary to previous observations, tumor cell death mainly occurred due to mitotic death rather than apoptosis. These results suggest an enhanced effect of HDR brachytherapy on radioresistant cells with the ability to impact the cell death pathway.(50)

Consequently, in most instances, administering radiation at a slower rate enables more effective cellular repair mechanisms to counteract radiation-induced damage. However, in certain cases, the opposite occurs. The inverse dose-rate effect, a phenomenon observed in radiation biology, demonstrates that biological damage from ionizing radiation increases as the dose rate decreases. This phenomenon is particularly relevant to specific cell types, including some mammalian and tumor cells, when irradiated at a narrow range of very low-dose rates, as illustrated in **Figure 1.9**.

DR to Acute radiation

DR to Continuous radiation

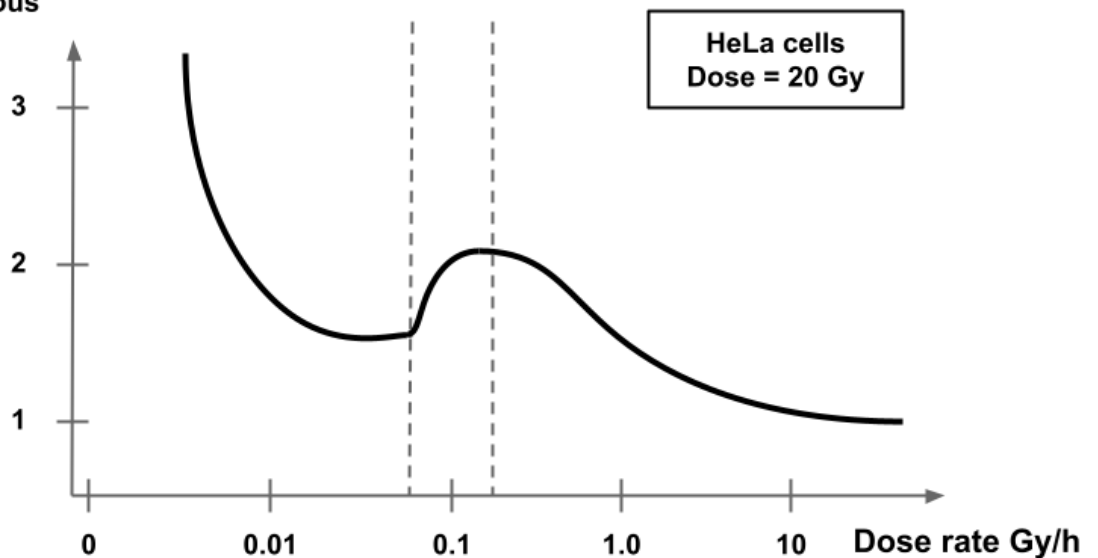


Figure 1.9. Dose-response ratios - acute to continuous irradiation function of the dose rate. Adapted from Leonard, 2007.(51) Idealized curve of dose-response ratios - acute to continuous irradiation as a function of dose rate, derived from HeLa cells exposed to a constant dose of 20 Gy. DR : dose-response.

The main mechanism involved is related to the cell cycle arrest in the G2 phase. When cells are irradiated at lower dose rates, they are more likely to recognize and repair DNA damage, leading to an accumulation of cells in the G2 phase. However, cells in the G2 phase are generally more radiosensitive compared to other phases of the cell cycle. As a result, when these G2-arrested cells are exposed to subsequent radiation doses, they are more prone to damage and cell death.(52)

1.2.4 Microenvironment

The tumor microenvironment (TME) includes the surrounding extracellular matrix, immune cells, fibroblasts, signaling molecules, and the blood vessels. During the last decade, the TME has been increasingly investigated and was shown to

contribute to cancer development and progression through complex interplays with tumor cells. To add to this complexity, TME may also play a role in tumor response after irradiation, for example through interactions between tumor cells and immune cells.(53)

Through immunosuppressive cytokine secretion, metabolic alterations, and other mechanisms, the TME provides a complex network that plays a role in tumor proliferation and immune evasion.(54) In order to restore antitumor immunity, immunotherapies are being introduced for the treatment of metastatic cancers. This success has led to a growing interest in combining immunotherapy with other therapeutic modalities.(55,56) The concept of a generalized immune-stimulatory effect for RT, more commonly referred to as the "abscopal effect" emerged as a hypothesis to explain the rare clinical observations of tumor response in metastases outside the radiation field. Preclinical models have shown that this effect is largely immune mediated.(57)

The effects of radiation therapy on the immune system can be divided into 4 key stages :

1. Priming of tumor antigen-specific T cells;
2. Immune cell infiltration into the tumor tissue;
3. Changes in the immunosuppressive TME (including local depletion of suppressive immune cell lineages)
4. Immunogenic modulation of the tumor cell phenotype, leading to an increased sensitivity of irradiated tumor cells to lymphocyte-mediated lysis.(58,59)

Combining immunotherapy and brachytherapy is a promising strategy; high radiation doses may be associated with a massive release of tumor associated antigens triggering a distant abscopal response.

Many tumor locations commonly treated with brachytherapy have been identified as good candidates for immunomodulation such as those anatomic sites dominated by human papillomavirus induced cancers. Preclinical trials have shown that human papillomavirus could lead to immune response evasion of cervical cancer

cells through the overexpression of the Programmed Death ligand 1 (PD-L1/PD-1) signaling pathway.(60) Those findings are in line with several clinical studies observing expression of PDL1 in cervical cancers ranging between 34.4% and 96%.(61–63)

The unequaled, high dose gradient attained with brachytherapy may be optimal for enhancing the immunogenic response at the irradiated site while minimizing antagonistic effects on peripheral immune cells by avoiding irradiation of draining lymph nodes.(64) The heterogeneity of the radiation dose delivered to the tumor is a crucial asset, allowing multiple immunogenic mechanisms corresponding to each distinct dose range, illustrated in **Figure 1.10**.

- Close to the source, exposure to hyperdoses results in a high rate of immunogenic tumor cell death followed by the release of tumor-specific antigens that are needed for the priming of T cells.(57)
- High-to-intermediate doses per fraction (5-12 Gy) may lead to immunogenic modulation by modifying the cell phenotype of surviving tumor cells.(65)
- Leukocyte infiltration in the tumor tissue enhanced by immune stimulatory cytokines may be attained using moderate doses per fraction (2-5 Gy).(66,67)
- Finally, local depletion of suppressive immune cell lineages (which are highly radiation-sensitive) can be achieved with low doses per fraction (1-2 Gy).(68,69)

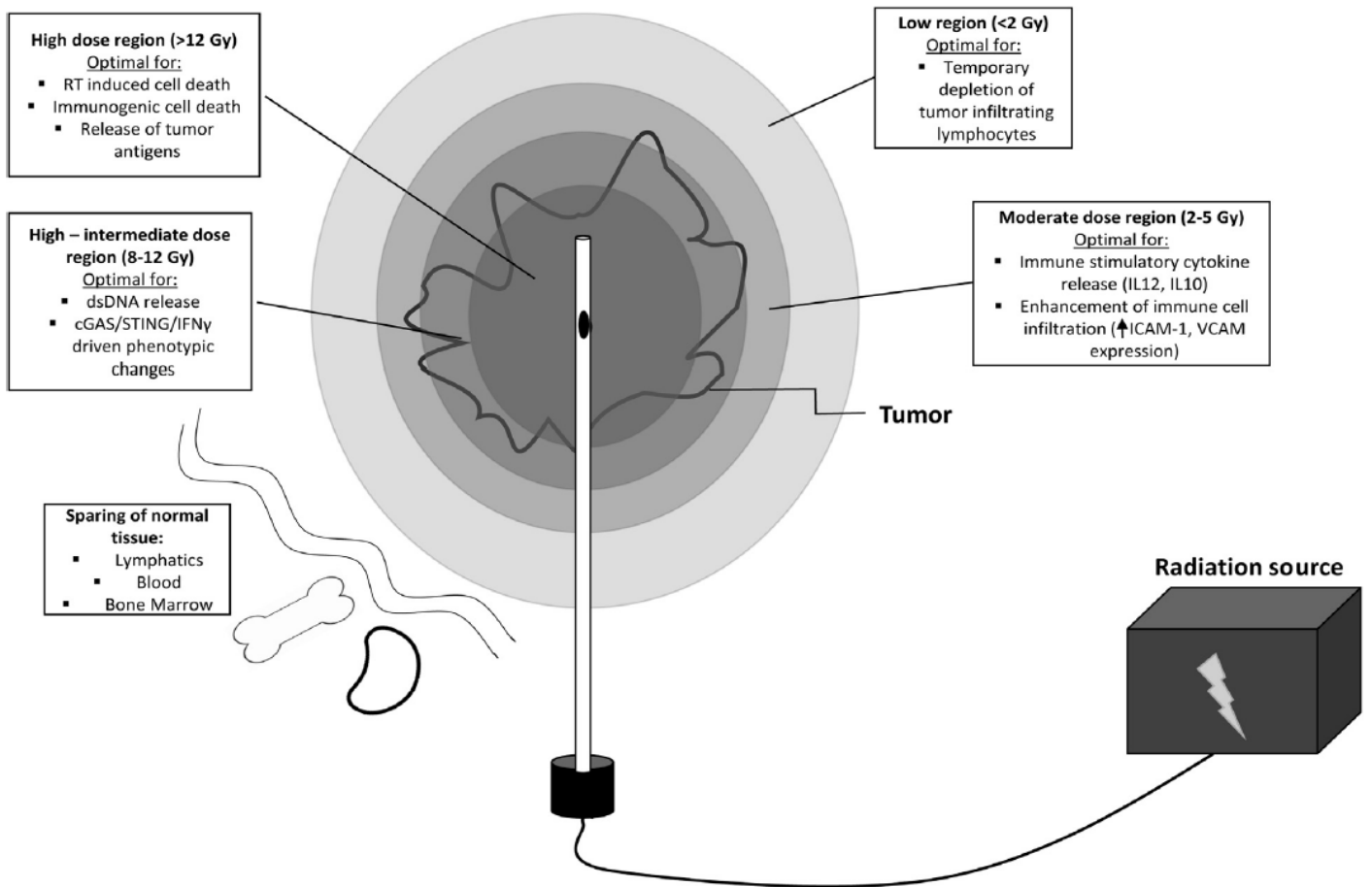


Figure 1.10. schematic representation of dose heterogeneity of brachytherapy delivery and its subsequent impact on the tumor microenvironment. From patel et al., 2018.(59)

Nevertheless, only a few preclinical studies have investigated the combination of brachytherapy and immunotherapy. Rodriguez-Ruiz et al. demonstrated that ^{192}Ir HDR brachytherapy (3 x 8 Gy per fraction) could lead to immunotherapy-potentiated abscopal effects in mice bearing subcutaneous colorectal carcinoma.(70) Hodge et al. observed that coupling tumor irradiation (8 Gy) either delivered locally with EBRT in a single fraction or implanting a single ^{125}I seed with a tumor-associated antigen vaccine drastically increased the occurrence of abscopal effects in mice transplanted with lung or colon adenocarcinomas.(71)

Immunomodulation is not the sole feature of the TME-brachytherapy interplay. Perfusion and partial pressure of oxygen (pO_2) modifications during EBRT have been suggested to play a key role in many preclinical and clinical studies. Variations in the TME vascularization or decreases in pO_2 are strong predictive factors of poor local

control.(72–75) The oxygen effect describes the heightened sensitivity of cells to ionizing radiation when oxygen is present. This phenomenon is vital in cancer treatment, as it influences therapeutic outcomes. During irradiation, oxygen molecules amplify the formation of reactive chemical species, also known as reactive oxygen species (ROS), which cause more severe DNA damage and diminish the likelihood of cellular repair. Exposure to ionizing radiation during radiotherapy significantly increases ROS production. This radiation induces the radiolysis of water molecules in and around cells, forming highly reactive free radicals such as hydroxyl radicals ($\bullet\text{OH}$), superoxide anions ($\text{O}_2^{\bullet-}$), and hydrogen peroxide (H_2O_2). These reactive species interact with biological macromolecules, including DNA, proteins, and lipids, inflicting oxidative damage. Molecular oxygen reacts with DNA radicals produced during radiation exposure, generating stable, irreparable DNA damage. This type of damage, referred to as the oxygen fixation hypothesis, reduces the chances of successful DNA repair and ultimately leads to cell death. Oxygen effect illustrated in **Figure 1.11**.

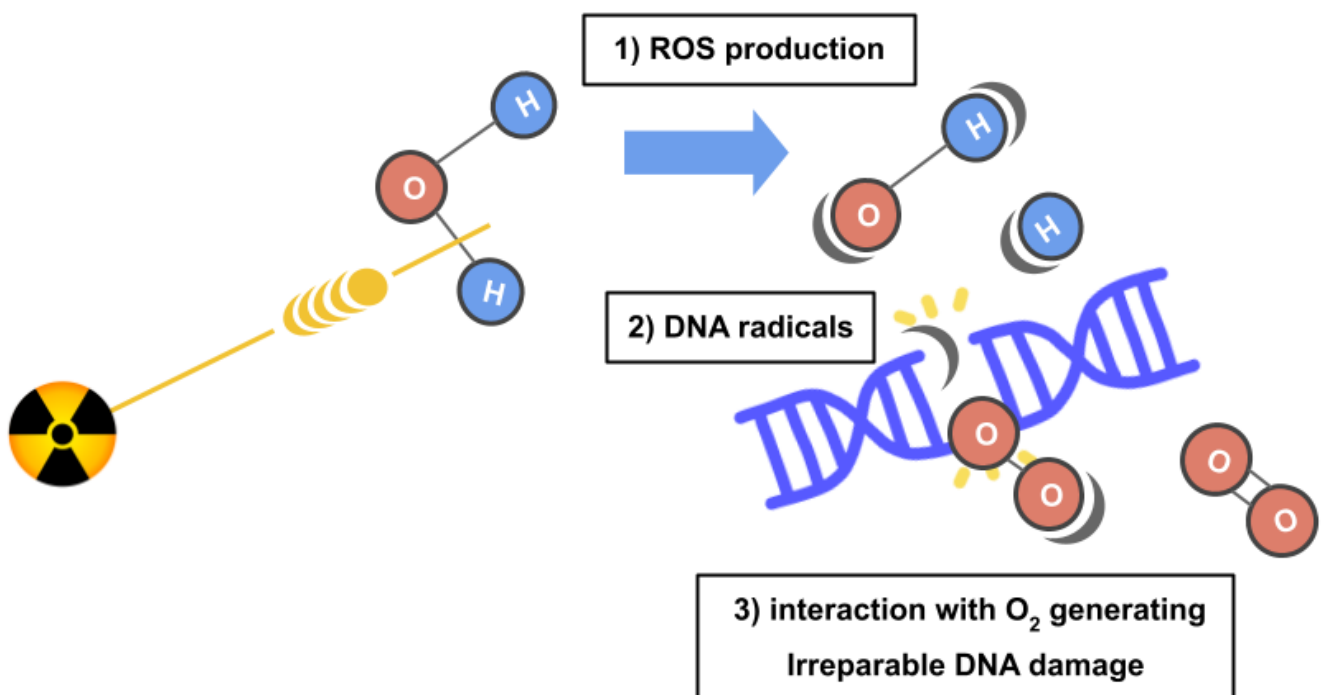


Figure 1.11. Illustration of the oxygen effect.

While scarce data are available regarding the impact of brachytherapy on tumor vascularization, some authors have observed an increase in TME pO_2 in experimental mouse tumors models treated with ^{125}I seeds.(76) Data suggest a greater oxygen effect with HDR brachytherapy vs LDR brachytherapy. Experiments on mammalian cell cultures irradiated with HDR brachytherapy (66 Gy/h) and LDR brachytherapy (0.32 Gy/h) showed that the oxygen enhancement ratio for HDR brachytherapy was approximately 2.4 vs 1.5 for LDR brachytherapy.(77,78)

Other factors related to the oxygen effect should be considered, such as the implantation technique itself. In a preclinical model, a decrease in perfusion and oxygenation after implantation of interstitial catheters in mice with subcutaneous rhabdomyosarcoma treated with HDR brachytherapy (^{192}Ir) was reported. While the median tumor pO_2 observed at baseline was 13.5 mm Hg, the pO_2 dramatically decreased at 1h (1.2 mm Hg) and only partial recovery was achieved at 24 hours (5.3 mm Hg). This suggests that the implantation of brachytherapy interstitial catheters could lead to local hypoxemia with a significant reduction in the radiation effect of a HDR brachytherapy treatment. Indeed, cell survival after irradiation (10 Gy) 1 to 24 hours after implantation suggest a decrease in pO_2 .(79) Although no clinical data corroborates these preclinical findings, such data suggest that an excessive delay between implantation of interstitial catheters and treatment may potentially affect treatment outcomes. This situation could potentially favor local resistance to radiation without the offset of hyperdose sleeves that could compensate for the hypoxic effect. However, this aspect of radiobiology is poorly understood.

1.2.5 Repopulation

Repopulation allows quiescent cells to re-enter mitosis and undergo repopulation (“normal” growth of surviving cells) or even accelerated proliferation as a response to the inflicted damage. This phenomenon is observed between treatment fractions but can potentially be present during continuous irradiation when the cell cycle effect is decreasing. This phenomenon could result in treatment failure if the delivered dose is not large enough to overcome the repopulation effect.

The effect of repopulation during protracted irradiation is expected to be negligible for dose rates greater than 0.3 Gy/h.(80) Repopulation in brachytherapy

has mostly been investigated for locally advanced cervical cancers treated with definitive chemoradiation. The first clinical evidence of accelerated repopulation onset time was reported by Huang et al.(81) Repopulation can occur during EBRT, as well as between EBRT and the initiation of brachytherapy, or between 2 HDR fractions. While the optimal fractionation for HDR has been the subject of many publications,(82) several large prospective and retrospective studies investigated the optimal overall treatment time between the start of EBRT and completion of brachytherapy.(83–85) Local control of locally advanced squamous cell carcinoma (eg, cervix, head, and neck carcinoma) was found to decrease by 1% per day when the overall treatment time (eg, for EBRT and brachytherapy) exceeded 50 days. Therefore, completing treatment in an appropriate time frame should be a priority in the management of patients with locally advanced cervical cancer.

1.3 Practical Applications

1.3.1 LDR vs HDR vs PDR

LDR brachytherapy was the original brachytherapy modality from which most radiobiological or clinical studies were developed. From a radiobiological point of view, nonclinical studies comparing the therapeutic ratio of HDR vs LDR found a theoretical advantage in favor of LDR.(86–88) Despite this finding, randomized trials, as well as meta-analyses on cervical cancer patients failed to show an increased risk of toxicity with HDR brachytherapy.(89–92) This may be due to the inherent ability to adjust dwell times and positions with HDR brachytherapy, leading to an optimized dose distribution counterbalancing its potential radiobiological disadvantages.

Furthermore, LDR brachytherapy originally utilized radium sources, with poorly adapted source lengths, and the sources were not fixed relative to one another resulting in poorer dose distributions than can be achieved with modern afterloaders and applicators. Therefore, these clinical studies introduce a bias when comparing treatments based on outdated optimization processes (LDR) to modern approaches based on stepping source technology (HDR). In fact, HDR brachytherapy was developed with the intent purpose to increase dose optimization capabilities and avoid the disadvantages of LDR in terms of radioprotection.(93,94)

For these reasons, HDR is often preferred worldwide over the other brachytherapy modalities, despite its theorized radiobiological inferiority as compared to LDR brachytherapy or PDR brachytherapy.

PDR brachytherapy was developed to combine the radiobiological advantage of LDR with the advantages introduced by HDR brachytherapy in terms of dose optimization and radioprotection. However, to our knowledge, only one prospective trial comparing HDR brachytherapy to PDR brachytherapy in patients with locally advanced cervical cancer was published. In this randomized study, three fractions delivering 7 Gy to “point A” were performed in the HDR arm while the PDR arm patients received a single session over 39 hourly pulses delivering 0.7 Gy/pulse. A trend in favor of PDR regarding toxicity was observed although statistical significance was not reached in this low powered study. The rates of late rectal grade ≥ 3 toxicity

and late bladder grade ≥ 2 toxicity were greater than 10% in the HDR arm while no toxicity was observed in the PDR arm, and the rate of late vaginal grade ≥ 2 toxicity was 15.8% in the HDR arm vs 5.6% in the PDR arm.(95)

Despite theoretical radiobiological advantages, the use of PDR-brachytherapy is decreasing worldwide due to logistic, regulatory, and economic reasons. However, PDR brachytherapy is still preferred when available for treating highly sensitive areas such as the anal canal, penile glans, vagina, and oral mucosa.(3,96,97) The brachytherapy community should therefore still promote PDR brachytherapy to maintain this treatment modality, especially for the treatment of pediatric cancers. To date, institutions have the ability to select their brachytherapy equipment modality (ie, VLDR, LDR, HDR, and PDR brachytherapy). Beyond the cost-utility perspective, this choice should account for the center's activity in terms of number of patients and intended type of treatments. Indeed, the radiobiological impact of dose rate is dependent on various factors including the target location (and its vicinity to OARs), the intrinsic sensitivity of the tumor, and the total delivered dose. For the few centers offering both PDR and HDR brachytherapy, some patients may benefit more from one modality over the other, allowing us to investigate further the concept of radiobiological optimization.

1.3.2 Radiobiology Modeling

It is challenging to understand the effects of exposure from a wide range of dose rates and varying brachytherapy modalities. To help physicians in daily practice, radiological models based on the linear quadratic model have been developed.(19,81,88,98–101) Reviews on how to use these models (and their validity limitations) have been previously published.(80,102,103) Biologic equivalent dose calculators are available, allowing one to estimate dose in equivalent 2 Gy dose fractions (EQD2) for tumors and normal tissues, according to various fractionations and various dose rates. Use of these types of calculators should be highly careful and modifications of fractionations in clinics should be based on published data reporting on safety and efficacy.(104)

In gynecological brachytherapy, EQD2 has been adopted by many brachytherapists to study outcomes and toxicities associated with HDR, LDR, and PDR treatments. However, for interstitial implants, the results from HDR brachytherapy should be used with caution given the close proximity of tissues to the source, and the higher dose heterogeneity as compared to intracavitary implants. Whether EQD2 calculations should be adjusted to correct for dose inhomogeneity is under investigation. The overall treatment time and time interval between fractions should also be investigated, as these factors will impact the radiobiological response.

The biologically effective dose for HDR brachytherapy is estimated following the same linear quadratic model used for EBRT with alpha/beta ratios (α/β ratio) derived from experimental and clinical data.(87,105) Radiobiological models predicting isoeffectiveness of LDR and PDR brachytherapy are based on incomplete repair model.

The capacity of PDR to better spare normal tissue, as compared to HDR brachytherapy, depends on tissue characteristic factors such as $T_{1/2}$ and the α/β ratio.(35,106) Based on preclinical studies and clinical observation, the Groupe Europeen de CurietherapieEuropean Society for Radiotherapy & Oncology (GEC ESTRO) recommends a $T_{1/2}$ of 1.5 h as a “best estimate” for normal tissue.(107) Other authors have reported preclinical data suggesting an underestimated $T_{1/2}$ of normal tissue, typically modeled as biphasic repair.(108,109) Biphasic repair is a concept used in radiobiology to describe the two distinct phases of cellular repair processes that occur after exposure to ionizing radiation. As illustrated in **Figure 1.12**, when cells are subjected to radiation, various types of DNA damage, such as single-strand breaks, double-strand breaks, and base modifications, can occur. The cellular repair mechanisms responsible for fixing this damage may follow a biphasic pattern, consisting of a fast and a slow component :

1. Fast component (about 0.14h) : This phase occurs immediately after radiation exposure and involves the rapid repair of relatively simple DNA lesions, such as single-strand breaks and base modifications. Repair mechanisms such as base excision repair (BER) and nucleotide excision repair (NER) are typically involved in this phase, which usually takes place within minutes to a few hours post-irradiation.

2. Slow component (about 2.7h): This phase involves the repair of more complex DNA damage, such as double-strand breaks, which require more time and intricate repair pathways to be fixed. The slow component can last from several hours to days after irradiation. Repair mechanisms such as homologous recombination (HR) and non-homologous end joining (NHEJ) are predominantly involved in this phase.

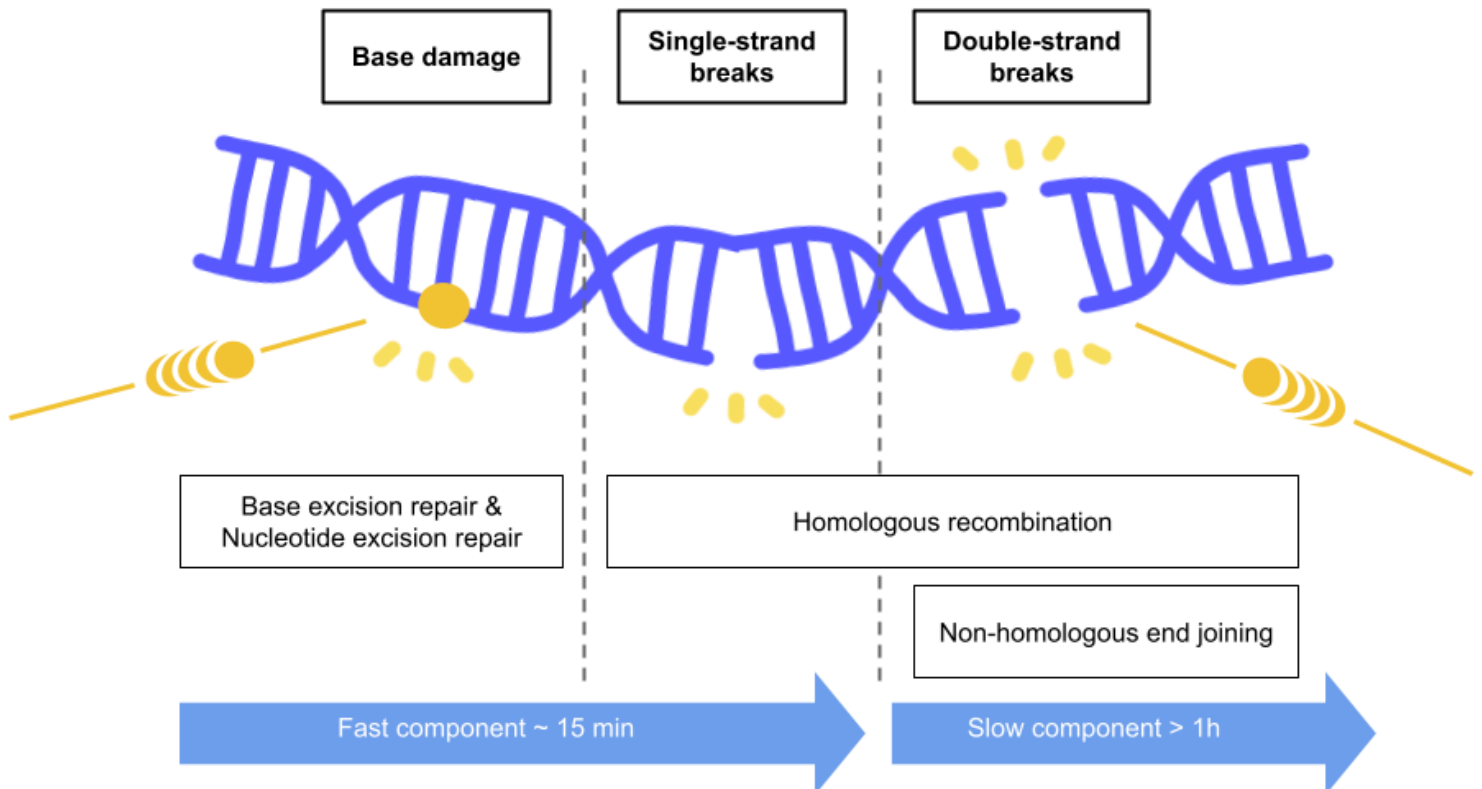


Figure 1.12. Biphasic repair concept, illustration adapted from Joubert et al.,2007.(110)

A subsequent clinical study corroborated this observation. In a secondary analysis of the CHART trial, investigating hyperfractionated EBRT for patients with head and neck cancer, the estimated repair halftime was 3.8 hours for laryngeal edema, 3.8 hours for skin telangiectasia, and 4.9 hours for subcutaneous fibrosis.(109) Clonogenic survival experiments can reflect the ability of cells to proliferate in vitro.(111)

Various methods have been proposed to estimate tumor and normal tissue equivalent doses, usually incorporating linear quadratic calculations which assume that tumor cells present the same response as cells in culture.(112) However, it is likely that such in vitro models incorporate a significant error in dose-effect estimation for tissue response. Another limitation is that equivalent doses are calculated only for several isodose levels (eg, prescription isodoses) and metrics, commonly the minimal doses to the most exposed 2cc (D2cc). As a consequence, it may underestimate dose response for tissues that reside close to the source. Moreover, it must be emphasized that the linear quadratic model has not been validated for doses exceeding 10 Gy per fraction.(108)

Against this backdrop of uncertainties, more empiric approaches have been proposed. Robust multimetric modeling approaches selecting several univariate-significant dosimetric features of the dose distribution, and medical variables (eg, tobacco use, vascular disease, age, and concurrent systemic agents) are increasingly used to estimate TCP and normal tissue complication probability. Such strategies may offset the weakness of radiobiological models which use regression analysis to fit clinical data. More advanced models use machine learning algorithms to determine the best combination of variables, optimizing prediction performance, and reproducibility.(113,114) The applicability of these algorithms has yet to be unequivocally demonstrated.

1.3.3 Dose Rate and Fractionation Optimization

Mathematical models have been developed to help determine the optimal HDR brachytherapy fractionation schemes.(115) Among the regimens tested, some are protracted over several weeks, delivering one fraction each week. Such fractionation schemes should be considered only in the adjuvant setting or for slowly proliferating tumors. From a radiobiological point of view, limiting the number of fractions and increasing the overall treatment time should lower the therapeutic index.

In cervical cancer, a large retrospective study based on 2D brachytherapy treatment planning concluded that HDR brachytherapy fractionation has a significant

effect on toxicity rates. The probability of severe morbidities was doubled when the dose/fraction to Point A exceeded 7 Gy (1.3% for doses ≤ 7 Gy vs 3.4% for doses > 7 Gy, p-value < 0.001).⁽¹¹⁶⁾ This study was, however, published at a time when only marginal physical dose optimization was possible, and therefore the correlation between point A dose per fraction and toxicity may reflect the overall irradiated volume.

Apart from normal tissue tolerance or local response, some authors have described a modification of biological response in patients with prostate cancer undergoing definitive HDR brachytherapy. Hauck et al. observed an increased incidence of prostate-specific antigen bounce with single-fraction HDR, as compared to regimens delivering the total dose over 2 or 3 fractions.⁽¹¹⁷⁾

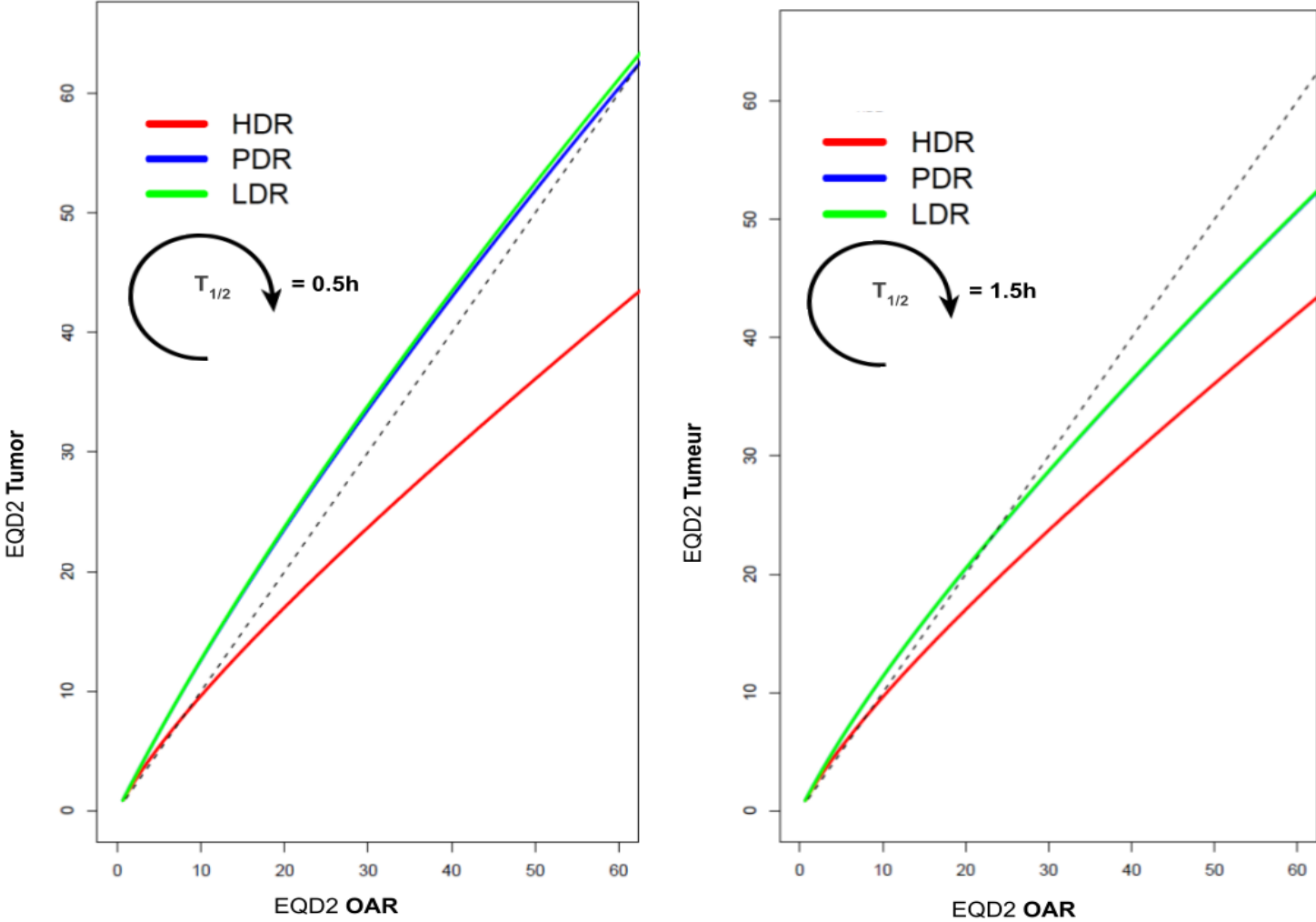
For LDR and PDR brachytherapy, dose rates to the target volume and OARs should be monitored. Regarding OARs, the dose rate should ideally not exceed 0.6 Gy/h. Above this threshold, some authors have observed an increasing rate of toxicity. In patients with squamous cell carcinomas of the mobile tongue and floor of mouth treated with interstitial LDR ^{192}Ir , dose rate greater than 0.5 Gy/h was significantly associated with an increased risk of necrosis.⁽²⁷⁾

For penile carcinoma patients, the risk of necrosis has been reported to be correlated with dose rate. Among patients with disease limited to the glans penis and receiving a dose < 65 Gy, the risk of painful ulceration was 6.5% for dose rates ≤ 0.42 Gy/h vs 30.7 % for dose rates > 0.42 Gy/h.⁽¹¹⁸⁾ In a phase III clinical trial including cervical cancer patients treated with brachytherapy followed by surgery, a higher prevalence of grade 2+ toxicities was observed when the dose rate increased from 0.4 to 0.8 Gy/h.⁽²⁵⁾

Conversely, decreasing dose rate to the target volume could lead to poorer local tumor control, and this is more likely for tumors with high sublethal damage repair capabilities. In a cohort of 340 patients with breast cancer receiving a brachytherapy boost, Mazon et al. observed a significantly higher local relapse rate in patients treated with dose rates ranging from 0.3 to 0.4 Gy/h (31%), as compared to patients treated with dose rates ranging from 0.8 to 0.9 Gy/h (0%). To maximize local control, the authors recommended a minimal dose rate of 0.6 Gy/h.⁽²⁵⁾

For the same indication and from a cohort of 289 patients, Deore et al. observed that the dose-rate should be maintained between 0.3 and 0.7 Gy/h to maximize local control and reduce the probability of late normal tissue injury.(119)

Figure 1.13 shows the variations of therapeutic index with brachytherapy modality, $T_{1/2}$, and α/β value.



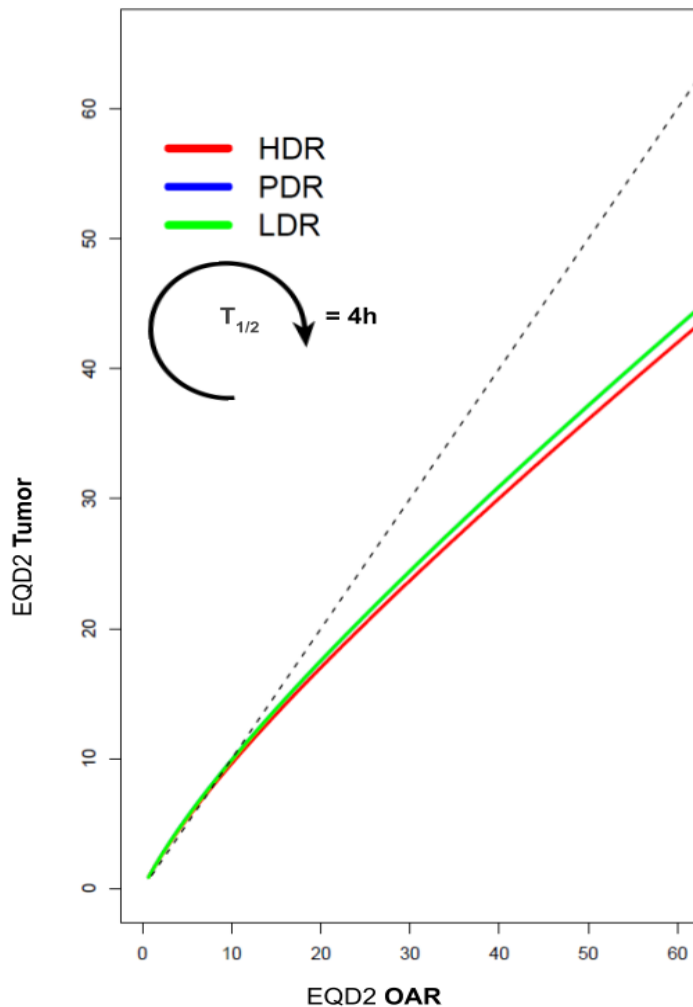


Figure 1.13 EQD2 to the tumor as the function of EQD2 to the OAR according to the linear quadratic model.

A graphical depiction of the variation of the therapeutic index based on brachytherapy modality, a/β ratio, and $T_{1/2}$ ranging from 0.5 h to 4 h. For this illustration, HDR brachytherapy, depicted in red, was intended to be delivered using four fractions delivered twice a day, PDR, depicted in blue, was delivered over 48 hourly pulses, and LDR shown in green, was delivered over 48 continuous hours. Note that with this setting, there is an overlap between the PDR and LDR curves. The abscissa (x value) represents the EQD2 of the OAR (a/β ratio = 3 Gy), whereas the ordinate (y value) represents the EQD2 of the tumor (a/β ratio = 10 Gy); the steeper the slope of the curve, the greater the expected therapeutic index.

Screening patients based on the expected dose contribution of brachytherapy to their OARs and target volume may allow for an increase in the therapeutic index, giving physicians the possibility to decide which brachytherapy modality is most appropriate. A study based on this approach has examined, in the setting of locally advanced cervical cancer (LACC) treated with brachytherapy after chemoradiation, how the therapeutic index could be modified using PDR brachytherapy instead of HDR brachytherapy. Optimization was intended to achieve the same minimal dose to 90% of the high-risk clinical target volume ($D_{90} \text{CTV}_{\text{HR}}$) EQD2 with HDR as with PDR. For the OARs, the effect of radiobiological weighting was dependent on the delivered dose. The higher the physical dose, the greater the radiobiological difference between the 2 brachytherapy modalities. When the brachytherapy contribution to OAR D2cc doses were <20 Gy EQD2, PDR and HDR brachytherapy were found to be equivalent, whereas, OARs EQD2 doses were all higher with HDR when the brachytherapy contribution to D2cc was ≥ 20 Gy, as seen in **Figure 1.14**.(15)

Nevertheless, this dosimetric study did not take into account the possibility to compensate for this radiobiological inferiority by optimizing dose distribution through an increasing use of interstitial needles. Further investigation is needed to implement such a strategy based on radiobiological optimization into daily practice. In addition, the validity of using the linear quadratic model at the range of doses used in HDR brachytherapy is debatable.

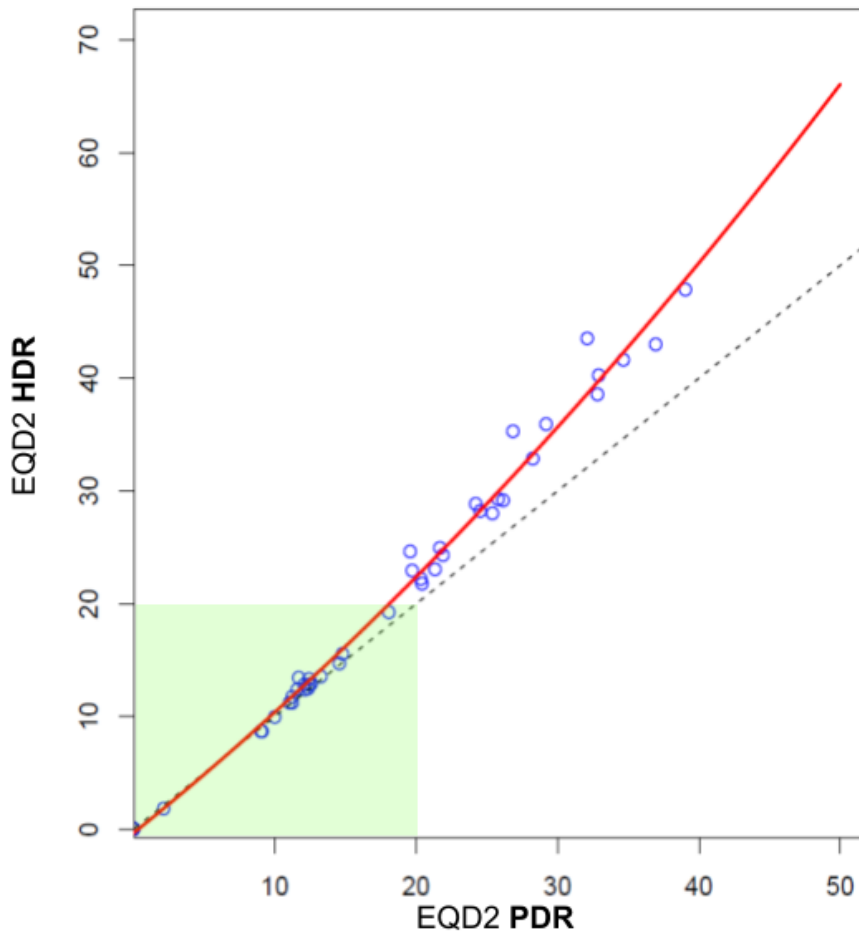


Figure 1.14. Comparison of EQD2 to OAR between HDR and PDR brachytherapy in locally advanced cervical tumor patients.

Each point represents a dosimetric variable for one patient. The abscissa represents the EQD2 of the PDR plan, whereas the ordinate represents the EQD2 of the HDR plan. HDR brachytherapy, intended to be delivered using four fractions delivered twice a day, PDR, was delivered over 48 hourly pulses. α/β ratio was considered equal to 3 Gy, and $T_{1/2}$ to 1.5h. When the point is above the dashed line, this means that the dose EQD2 is higher in the HDR plan.

1.3.4 Pharmacomodulation

Pharmacomodulation relies on the delivery of a systemic treatment aimed at modifying biological radiation effects. The outcomes of external beam radiotherapy for the treatment of locally advanced tumors (eg, cervical cancer, malignant glioma,

non-small cell lung cancer, head and neck cancer, and anal cancer) were shown to significantly improve with the addition of concurrent chemotherapy, and as such, concurrent chemoradiation is now considered standard of care for most sites where radiotherapy plays a major curative role in the treatment of bulky tumors.(120)

Chemotherapy

To date, there is no strong evidence suggesting that concomitant chemotherapy improves outcomes when given with brachytherapy. Only a few clinical studies combining chemotherapy with brachytherapy have been published.

A retrospective study of 372 patients investigated the use of concomitant chemotherapy with vaginal brachytherapy in the treatment of endometrial cancer. After hysterectomy, patients underwent EBRT followed by vaginal brachytherapy with concurrent carboplatin and paclitaxel based chemotherapy. The mean brachytherapy dose was 15.08 Gy delivered over 3-4 weekly fractions. A good tolerance profile was observed without any in-field grade ≥ 3 toxicities. Efficacy data were not reported, but overall treatment time was decreased by 4 weeks (p-value < 0.001).(121)

The Radiation Therapy Oncology Group 9207 reported on a phase I/II trial of patients treated with EBRT, brachytherapy, and concurrent cisplatin and 5-fluorouracil-based chemotherapy for localized esophageal cancer. An EBRT dose of 50 Gy (25 fractions given over 5 weeks) was delivered followed by brachytherapy. The objective of the trial was to determine feasibility and toxicity of chemoradiation in patients with adenocarcinoma or squamous cell carcinoma of the esophagus. brachytherapy was delivered using either 15 Gy delivered in 3 weekly fractions with HDR, or 20 Gy delivered in a single LDR temporary implant. The authors described a high rate of severe toxicity including a fistula incidence of 12%. Three patients (among the 49 included) died of radiation toxicity. However, due to the single-arm design of the study, one cannot conclude that the complications were due to the combination of chemotherapy and brachytherapy. Comparison with other clinical data based on EBRT +/- concurrent chemotherapy suggest that dose escalation itself could be the cause of this high toxicity rate.(122)

A meta-analysis of trials comparing ^{125}I brachytherapy with chemotherapy in advanced non-small cell lung carcinoma identified 15 studies including 1188 cases.

The authors found significant differences in overall response rates and disease control rates between patients treated with ¹²⁵I brachytherapy combined with chemotherapy vs chemotherapy alone. A higher risk of pneumothorax, bloody sputum, and pneumorrhagia was observed in the combination cohort vs those patients treated with chemotherapy alone.(123)

A prospective study was conducted on 23 previously untreated patients with unresectable locally advanced head and neck cancer treated with brachytherapy and concomitant docetaxel, cisplatin, and 5-fluorouracil based chemotherapy. LDR ¹²⁵I seeds were implanted in the primary tumor in order to achieve a V90 (percent volume receiving 90% of the prescribed dose) of 90% to the tumor volume. The 2-year progression-free survival was 60.9% and no unexpected toxicity was mentioned.(124)

Strnad et al. reported on a retrospective study of 104 patients treated with PDR brachytherapy (median total dose of 65 Gy) for recurrent head and neck cancer, including 58 who were treated with concurrent chemotherapy. A 10-year local control of 76% was reported for the patient cohort treated with concurrent chemotherapy vs 39% for the other groups (p-value = 0014). In the overall population, soft tissue necrosis or bone necrosis was observed in 17.3% of the patients. No specific data regarding toxicity related to the concurrent chemotherapy group was described.(7)

It appears that simultaneous chemotherapy could be feasible in combination with brachytherapy. These results encourage further investigation, but a high level of evidence is still lacking to demonstrate safety and/or a specific benefit of adding concurrent chemotherapy to brachytherapy.

Immunotherapy

Based on the enthusiasm for radioimmunotherapy combinations, a few ongoing clinical trials are testing interstitial and intracavitary brachytherapy with immune checkpoints inhibitors. The NCT02635360 (ClinicalTrials.gov Identifier) phase II study aims to evaluate the safety and effectiveness of the PD-1 inhibitor, pembrolizumab in combination with chemoradiation for the treatment of locally advanced cervical cancer. The ATEZOLACC trial (NCT03612791) is a randomized phase II study assessing the PD-L1 immune checkpoint inhibitor atezolizumab in

locally advanced cervical cancer receiving concurrent chemoradiation and brachytherapy.

Androgen Deprivation Therapy

Preclinical studies have investigated the radiobiological impact of androgen deprivation. Regarding brachytherapy, in vitro experiments were performed on androgen-sensitive human prostate adenocarcinoma (LNCaP) cells. ^{137}Cs irradiation (3.6 Gy/min) was administered in a single fraction (ranging from 2 to 6 Gy) with and without androgen deprivation. Although an increased rate of apoptosis was observed in cells with androgen deprivation, there was no difference in clonogenic cell survival, suggesting a shift in the modality of cell death.(125) Bicalutamide (an antiandrogen) has been tested on LNCaP cells undergoing a single fraction (ranging from 1 to 8 Gy) of ^{137}Cs irradiation (1 Gy/min). An antagonistic radiation–drug interaction (eg, a protective effect of irradiation of cells expressing androgen receptor exposed to bicalutamide) was observed. This effect could be explained by the halt of LNCaP in the G1 phase.(126)

Contrary to in vitro experiments, a radio sensitization effect of androgen deprivation has been shown in mice with prostate tumor xenografts. A 2 field irradiation technique was utilized and delivered in a single fraction. Androgen deprivation was obtained using orchiectomy at different time points (12 days before, 1 and 12 days after irradiation). A decrease in the radiation dose required to control 50% of the tumor (TCD_{50}) was observed in mice undergoing orchiectomy. The radio sensitization effect was dramatically improved with the addition of neoadjuvant androgen deprivation (12 days before radiation).(127) Different outcomes were observed with fractionated irradiation. The combination of androgen deprivation and 2 Gy fractionated radiotherapy resulted in a supra-additive enhancement in tumor growth delay although no supra-additive apoptotic response was observed. Several mechanisms could be involved in the interaction between androgen deprivation therapy and radiation such as hypoxia.(128) It has been shown that androgen deprivation inhibits double-strand break repair and counterbalances the radioresistance promoted by the activation of androgen receptor due to irradiation.(129)

While clinical trials have demonstrated an improvement in overall survival in patients treated with hormonal therapy administered concurrently with EBRT for locally advanced prostate cancer, clinical evidence is lacking in the setting of early stage prostate cancer treated with brachytherapy. Nevertheless, neoadjuvant hormonal therapy and brachytherapy is widely used in early stage prostate cancer. This strategy is performed to downsize the prostate and overcome anatomical limitations, and could lead to a lower probability of urinary morbidity by decreasing the irradiated volume.(130) A retrospective study of 300 patients with early stage prostate cancer treated with 3 months of androgen deprivation therapy prior to brachytherapy reported no long-term effects from the hormonal therapy in terms of quality of life and bladder toxicity.(131)

Theranostics

“Theranostic” (“therapeutics” + “diagnostics”) approaches that combine therapeutic and imaging strategies, are currently under investigation in a phase I clinical trial evaluating the safety and tolerability of gadolinium based nanoparticles in combination with EBRT, concurrent chemotherapy, and brachytherapy in patients with locally advanced cervical cancer. The aim of the strategy is to increase the radiation effect in a very focal manner using secondarily emitted particles following the interaction of nanoparticles with incident photons. Additionally, this technique may assist in identifying subvolumes to guide dose escalation.

Hyperthermia

Local hyperthermia (HT) can be delivered with microwaves, radio waves, or ultrasound generating centrally focused energy in the target volume. Following tumor localization, superficial applicators or intraluminal/interstitial applicators can be applied. Regional HT can be administered using several methods such as regional perfusion, hyperthermic intraperitoneal chemotherapy, or with external devices using magnetic fields with or without magnetic particles.(132–135) Hyperthermic tissue (temperatures range between 40°C and 48°C) has been shown to act synergistically with radiation therapy, enhancing the radiation response by a factor of 1.4-2.1.(136)

Several mechanisms are believed to be responsible for this enhanced response and have been investigated in preclinical studies. HT induces blood

vessels dilatation around the tumor and makes cells more sensitive to RT due to the oxygen-effect.(137) Hyperthermia also inhibits DNA repair after radiation induced DNA damage.(138) Radiosensitizing effects are maximum when radiation and HT are delivered simultaneously or within several minutes of one another.(139) Clinical efficacy and safety of locoregional HT adjuvant to EBRT has been shown in large prospective randomized trials, notably in patients with pelvic malignancies.(140,141)

Few studies have been performed examining clinical applications of brachytherapy with concurrent HT. In a retrospective study of 76 prostate patients treated with a HDR brachytherapy boost (21 Gy in 2 fractions, except for 1 patient who received 19.5 Gy in 2 fractions) and interstitial HT, no ≥ 3 grade genitourinary or gastrointestinal toxicities were observed over a median follow-up of 26.3 months, while only 1 patient experienced local relapse.(142)

1.4 Summary and outlook

The dose/rate effect has been the most extensively researched radiobiological parameter within the context of brachytherapy treatments, with limited data available supporting the influence of other radiobiological factors underlying brachytherapy's effects. Preclinical studies have confirmed the theoretical radiobiological superiority of PDR brachytherapy.

Biological models based on the linear quadratic model and the incomplete repair model offer estimations of the optimal settings for brachytherapy modalities, while predictive models exist to evaluate the probability of normal tissue complications and local tumor control. Combining these two approaches may be helpful in determining the most appropriate brachytherapy modality for specific situations.

Nonetheless, it is essential to balance radiobiological models against the limited clinical data, uncertainties in determining their parameters, and the evolution of techniques. Acquiring more data to evaluate the applicability of these findings in practice is of paramount importance.

2 PDR Brachytherapy: Does Clinical Evidence Support Radiobiological Models?

2.1 Background

In the context of investigating the potential benefits of PDR brachytherapy and obtaining clinical evidence of PDR superiority, we chose to focus on anal canal cancer for several reasons. Firstly, this location provides one of the largest amounts of clinical data comparing PDR and HDR brachytherapy. Secondly, the brachytherapy implants used in anal canal brachytherapy are placed inside the main organ at risk, making it a more relevant model for evaluating the radiobiological sparing effects of PDR. Thirdly, colostomy-free survival rate is a reliable endpoint even in retrospective studies, allowing for a more accurate assessment of the therapeutic impact. Finally, contrary to LACC brachytherapy, the technology and methods used in both PDR and HDR anal canal brachytherapy have not changed dramatically in recent years, ensuring that any observed differences are likely due to differences in radiation dose rates delivered. Taken together, these factors make it more likely to achieve statistically significant results compared to other locations.

This work was conducted in collaboration with the GEC ESTRO PDR Task Force, which aims to gather recent data that could help redefine the role of PDR in the world of modern brachytherapy.

2.2 Brachytherapy boost in anal canal cancer – A GEC ESTRO PDR task force meta-analysis

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2.2.1 ABSTRACT

Purpose : A meta-analysis is presented comparing clinical outcomes and toxicities between high dose rate (HDR) and pulsed dose rate (PDR) brachytherapy (BT) for anal cancer.

Methods and material : Retrospective or prospective clinical trials were identified on electronic databases. Data were collected per Preferred Reporting Items for Systematic Reviews and meta-Analyses guidelines. Pooled effect size for HDR and PDR BT were compared using subgroup analyses.

Results : Nine retrospective studies with a total of 481 patients treated were included of which 219 with HDR and 262 with PDR. Significant differences were observed between the two groups for baseline characteristics and treatment. The cumulative proportion of stage T3-T4 was lower in the HDR group, 0.15 [95 % confidence interval (CI) 0.07–0.29] vs 0.27 [95 %CI 0.09–0.57] in the LDR group, $p < 0.001$. Lower BT doses (in equivalent 2- Gy fraction dose) were given for patients in the HDR group, 11.9 Gy [95 %CI 8.2–15.5] vs 19.5 Gy [95 %CI 15.0–24.0] in the PDR group, $p < 0.001$. No significant differences were found for clinical outcomes or toxicities. The pooled effect size of the overall survival at 5 years for HDR and PDR was respectively 0.82 [95 %CI 0.70–0.94] and 0.82 [95 %CI 0.73–0.91], $p > 0.99$. The 5 years local control was 0.86 [95 % confidence interval (CI) 0.81–0.91] and 0.83 [95 %CI 0.77–0.89], $p = 0.62$. Cumulative toxicity-related colostomy proportion was 0.04 [95 %CI 0.02–0.09] and 0.03 [95 %CI 0.02–0.07], $p = 0.85$.

Conclusion : Both modalities provided a good profile of tolerance and are effective organ conservative strategies for patients with anal canal cancer. In parallel with ongoing developments to better determine the optimal fractionation and dose for HDR-BT treatments, especially in large tumors, PDR BT still has a crucial role for dose escalation strategy in advanced cases.

Keywords : brachytherapy; anal cancer; High-dose rate brachytherapy; pulse dose rate brachytherapy; toxicity; local control

2.2.2 Introduction

Definitive radiotherapy and concomitant chemotherapy plays a major role in the treatment of anal canal cancer and represents the standard of care of cancer stage II-III of anal margin and stage I-III of anal canal(143). However, the dose for a boost after 50 Gy as well as the place and the modality of brachytherapy are still under debate.

Brachytherapy gives the possibility to focally increase the dose to the tumor while sparing organs at risk, including non-involved parts of the anal canal(144). Historically, brachytherapy boost was delivered through continuous LDR irradiation, because radiobiological grounds allow for optimal normal tissue sparing. HDR brachytherapy and PDR brachytherapy have progressively replaced LDR brachytherapy. HDR brachytherapy shows physical advantages, compared to Iridium 192 wires (better dose optimization, radiation safety, and short treatment time)(97).

Pulsed-dose rate brachytherapy combines physical advantages of HDR and radiobiological advantages of LDR brachytherapy. In PDR, instead of delivering the dose continuously as in LDR, a series of hourly HDR pulses, continuing few minutes each hour, is delivered. Typically, the overall dose and treatment time are the same as the corresponding LDR schedule. PDR compared to LDR has many distinct advantages such as isodose optimization, better therapeutic ratio attributed to multiple fractionation regimens as well as excellent radiation protection(31,145).

From a logistic point of view, the main disadvantage of the PDR compared to the HDR is the need for a hospital room equipped with a remote control afterloading system. Therefore it should increase cost and limit the possible number of brachytherapy procedures that can be performed daily.

Since no large randomized trials exist, it is difficult to compare efficacy and toxicity profiles of PDR brachytherapy and HDR brachytherapy. The aim of this study was to explore the literature performing a systematic review and meta-analysis.

2.2.3 Materials and methods

Protocol

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement (146). A systematic search was conducted by two investigators in Cochrane Central Register of Controlled Trials, PubMed, and Google Scholar until July 2021 for studies assessing the treatment outcomes of HDR and PDR brachytherapy boost for patients with anus neoplasm. We have used the following terms:

((“anus neoplasms” [MeSH Terms]) OR ((“anal” [All Fields] OR “anus” [All Fields]) AND (“cancer” [All Fields] OR “neoplasm” [All Fields]))) AND (“brachytherapy” [MeSH Terms] OR “brachytherapy” [All Fields]).

Study selection

To be included, studies should be prospective or retrospective, with more than 20 patients by brachytherapy modalities (e.g. HDR or PDR) and with at least 24 months of median follow-up time. In all cases, patients received brachytherapy as a boost. Studies without details on baseline characteristics, survival and toxicity provided separately for each brachytherapy modalities were excluded. Were also excluded: groups undergoing local excision prior to radiation therapy, intraluminal brachytherapy and association with other experimental treatment. In the studies with other groups of treatments (i.e. EBRT boost), we included only the groups that fulfilled the criteria above mentioned. Flowchart in **Figure 2.1**. Studies included are listed in **Table 2.1**.

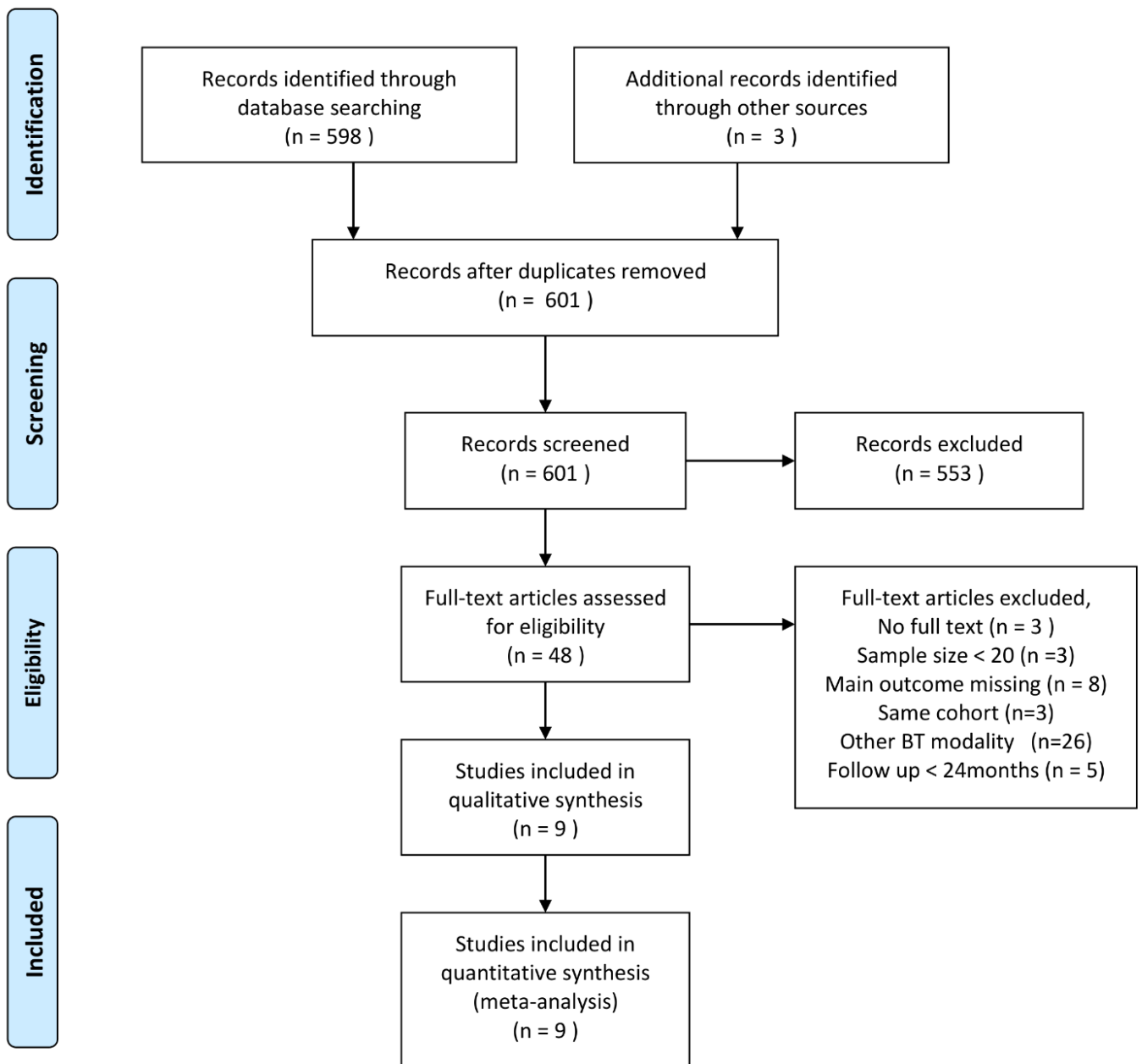


Figure 2.1. PRISMA flow diagram illustrating the systematic process conducted to select data.

BT: brachytherapy

Authors, year of publication	BT modality	Country	Mono/mult icentric	Median FU (years)	Patients' characteristics			Tumor characteristics	
					Number	% male	Age (median)	% T ₃ -T ₄	% N ₁ -N ₃
Karin Sigrid Kapp, 2001	HDR	Austria	monocentric	31	39	23.1	59	25.6	20.5
Julius Marek Doniec, 2006	HDR	Germany	monocentric	34	50	20.0	64	16.0	30.0
Christoph Oehler-Jänne, 2007	HDR	Switzerland	monocentric	60	34	11.8	60.4	29.4	26.5
Emilien Bertin, 2018	HDR	France	monocentric	61	46	19.6	65	4.3	13.0
Leonel Varela Cagetti, 2019	HDR	France	monocentric	33	50	16.0	67	6.0	6.0
Antoine Bruna, 2006	PDR	Belgium, France	multicentric	28.5	71	15.5	61.2	22.5	26.8
Thomas Gryc, 2016	PDR	Germany	monocentric	60	47	29.8	60	55.3	34.0
Alessandra Arcelli, 2019	PDR	Italy	monocentric	71	102	29.4	61	38.2	52.0
Remi Bourdais, 2021	PDR	France	monocentric	60.4	42	16.7	69	4.8	11.9

BT : brachytherapy, FU : follow-up, HDR : high dose rate, PDR : pulsed dose rate

Table 2.1. Patient and tumor characteristics.

Outcomes

Primary outcome was the proportion of toxicity-related colostomy. Secondary outcomes included proportion of toxicity grade 3 or more, 5-years colostomy-free survival rate, 5-years local recurrence-free survival rate, 5-years disease-free survival rate and 5-years overall survival rate. Survival data were extracted from the Kaplan Meier curve for each study using WebPlotDigitizer(147).

Clinical & treatment data

The variables that were likely to affect clinical outcomes were collected such as :

- 1) patient's characteristics: gender, mean age, mean follow-up time;
- 2) tumor's characteristics: T and N classification according to the Union for International Cancer Control (UICC), histology;
- 3) treatment characteristics: mean brachytherapy dose, volume related to the prescription dose, rate of concurrent chemotherapy and EBRT technics. If not available, mean and standard deviation (SD) were estimated following the method described by Hozo et al. (148) EQD2 dose was estimated using the linear quadratic model ; i.e. α/β ratio = 10 Gy (for tumor), $T_{1/2} = 1.5$ h.

Data synthesis and analysis

Proportions were logit-transformed before the meta-analysis and then pooled using a random effect model. Between-group mean differences were pooled with an inverse variance method using a random effect model. Pre-calculated effect sizes of survival data were estimated for each study and then pooled using a random effect model. To explore the differences between HDR and PDR groups, a subgroup analysis method was performed. In all analyses, a p-value < 0.05 was considered statistically significant. The meta-analysis was performed using the RStudio open software with “meta” and “metafor” R packages(149–151).

2.2.4 Results

Patient and tumor characteristics

Nine retrospective studies with a total of 481 patients were included of which 219 treated with HDR and 262 treated with PDR (152–160). The overall time period for all included studies ranged from 2001 to 2021. Mean follow-up time was significantly shorter in the HDR group, 51 months [IC95%, 33 – 68] versus (vs) 71 months [IC95%, 20 – 122] in the PDR group, $p < 0.001$. Mean age was respectively 61 years [IC95%, 59 – 63] and 60 years [IC95%, 58 – 62], $p = 0.84$. Gender ratio (male/female) was respectively 0.19 [IC95%, 0.13 – 0.26] and 0.24 [IC95%, 0.18 – 0.30], $p = 0.22$.

Proportion of stage T3 and T4 was significantly lower in the HDR group, 15 % [IC95%, 7 – 29] vs 27 % [IC95%, 9 – 57] in the PDR group, $p < 0.001$. Patient and tumor characteristics are described in **Table 2.1**.

Treatment characteristics

Eight studies reported a prescription to the 85 % reference isodose. One study didn't report it. (155) No study reported the volumes of the prescription isodose. Mean brachytherapy EQD2 dose was significantly lower in the HDR group, 11.9 Gy [IC95%, 8.2 – 15.5] vs 19.5 Gy [IC95%, 15.0 – 24.1] in the PDR group, $p < <0.001$. Alternative EQD2 estimation, with another α/β ratio and $T_{1/2}$, is detailed in **Table 2.2**. Proportion of intensity-modulated radiation therapy (IMRT) treatment was significantly higher in the HDR group, 15 % [IC95%, 3–51] vs 4 % [IC95%, 0–61] in the PDR group, $p < 0.01$. Proportion of concomitant chemotherapy was significantly lower in the HDR group, 70 % [IC95%, 61–77] vs 81 % [IC95%, 33–97] in the PDR group, $p < 0.01$. Treatment characteristics are described in **Table 2.3**.

HDR studies	ab	3			7			10		
Karin Sigrid Kapp 2001		17.6			13.3			12		
Julius Marek Doniec 2006		14.2			12.0			11.4		
Christoph Oehler-Jänne 2007		14			14			14		
Emilien Bertin 2018		18.2			16.3			15.8		
Leonel Varela Cagetti 2019		21.5			18.1			17.1		

PDR studies	ab	3			7			10		
	T_{1/2}	0.5	1.5	4	0.5	1.5	4	0.5	1.5	4
Antoine Bruna 2006		18.0	26.2	43.2	19.6	24.2	33.6	20.1	23.6	30.6
Thomas Gryc 2016		11.1	14.6	21.9	12.9	14.8	18.9	13.4	14.9	18.0
Alessandra Arcelli 2019		16.1	22.2	35.5	18.1	21.5	28.9	18.8	21.3	26.9
Remi Bourdais 2021		14.6	19.0	29.0	17.0	19.4	25.0	17.7	19.6	23.7

HDR : high dose rate, PDR : pulsed dose rate, ab : alpha/beta ratio, T_{1/2} : repair halftime

Table 2.2. Alternative EQD2 estimation.

Authors, year of publication	BT			EBRT		
	Dose rate	Mean eqd2 (Gy) with sd	Median BT to EBRT gap (day)	Median total /fraction dose (Gy)	%IMRT	% Concomitant chemotherapy
Karin Sigrid Kapp, 2001	HDR	8 (1.5)	17	50.4/1.8	0	71.8
Julius Marek Doniec, 2006	HDR	9.3 (1.0)	42	45/1.8	0	-
Christoph Oehler-Jänne, 2007	HDR	14 (0.7)	21	45/1.8	0	79.4
Emilien Bertin, 2018	HDR	14 (0.8)	17	45/1.8	54.3	71.7
Leonel Varela Cagetti, 2019	HDR	14 (2.0)	16	45/1.8	74.0	60.0
Antoine Bruna, 2006	PDR	21.1 (2.0)	29	45/1.8	-	-
Thomas Gryc, 2016	PDR	15.1 (7.6)	40	53.5/1.8	2.1	89.4
Alessandra Arcelli, 2019	PDR	20.7 (2.3)	-	45/1.8	0	94.1
Remi Bourdais, 2021	PDR	20 (5.8)	23	44/2	45.2	38.1

BT : brachytherapy, EBRT : external beam radiation therapy, HDR : high dose rate, PDR : pulsed dose rate, sd : standard deviation, IMRT : Intensity-modulated radiation therapy

Table 2.3. Treatment characteristics.

Survival outcomes

All but one study reported survival data of local recurrence. Five-years local recurrence-free survival rates for HDR and PDR groups were respectively 85.6 % [IC95%, 80.7 – 90.5] and 83.0 % [IC95%, 77.0 – 89.1 %], $p = 0.52$. Corresponding forest plot in **Figure 2.2**. Six studies reported the colostomy-free survival rate. Five-years colostomy-free survival rates were respectively 79.6 % [IC95%, 71.4 – 87.8] and 76.4 % [IC95%, 53.6 – 99.2], $p = 0.79$. Six studies reported the disease-free survival rate. Five-year disease-free survival rates were respectively 73.5 % [IC95%, 66.1 – 81.0] and 72.4 % [IC95%, 55.6 – 89.3], $p = 0.90$. Seven studies reported the overall survival rate. Five-year overall survival rates were respectively 81.9 % [IC95%, 70.3 – 93.5] and 82.0 % [IC95%, 72.6 – 91.4], $p < 0.99$.

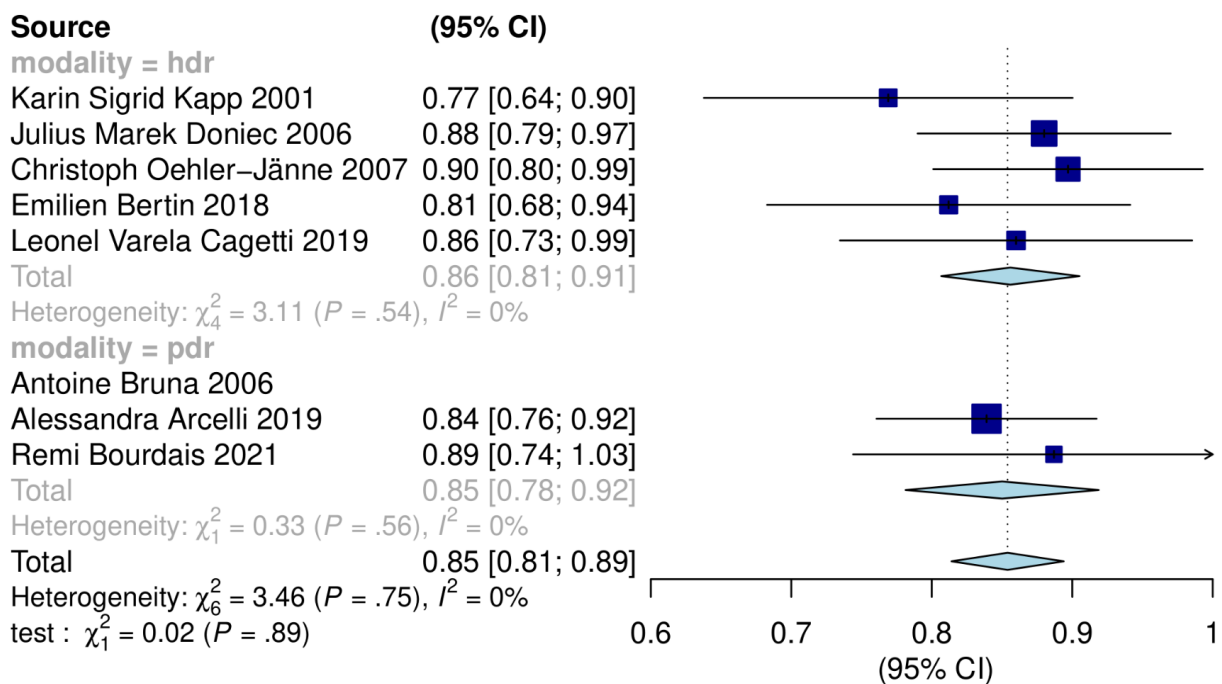


Figure 2.2. Forest plot of five-year local recurrence-free survival rate. HDR: high dose rate, PDR: pulsed dose rate, CI: confidence interval

Toxicities

All studies reported the number of toxicity-related colostomies. Proportion of toxicity-related colostomy in the HDR group was 4 % [IC95%, 2–9] vs 3 % [IC95%, 2 – 7] in the PDR group, $p = 0.67$. Corresponding forest plot in **Figure 2.3**. Seven studies reported the number of pelvic late toxicity grade 3 or more (including colostomy). Proportion of pelvic late toxicity grade 3 or more was respectively 7 % [IC95%, 4 – 12] vs 10 % [IC95%, 4 – 26], $p = 0.25$.

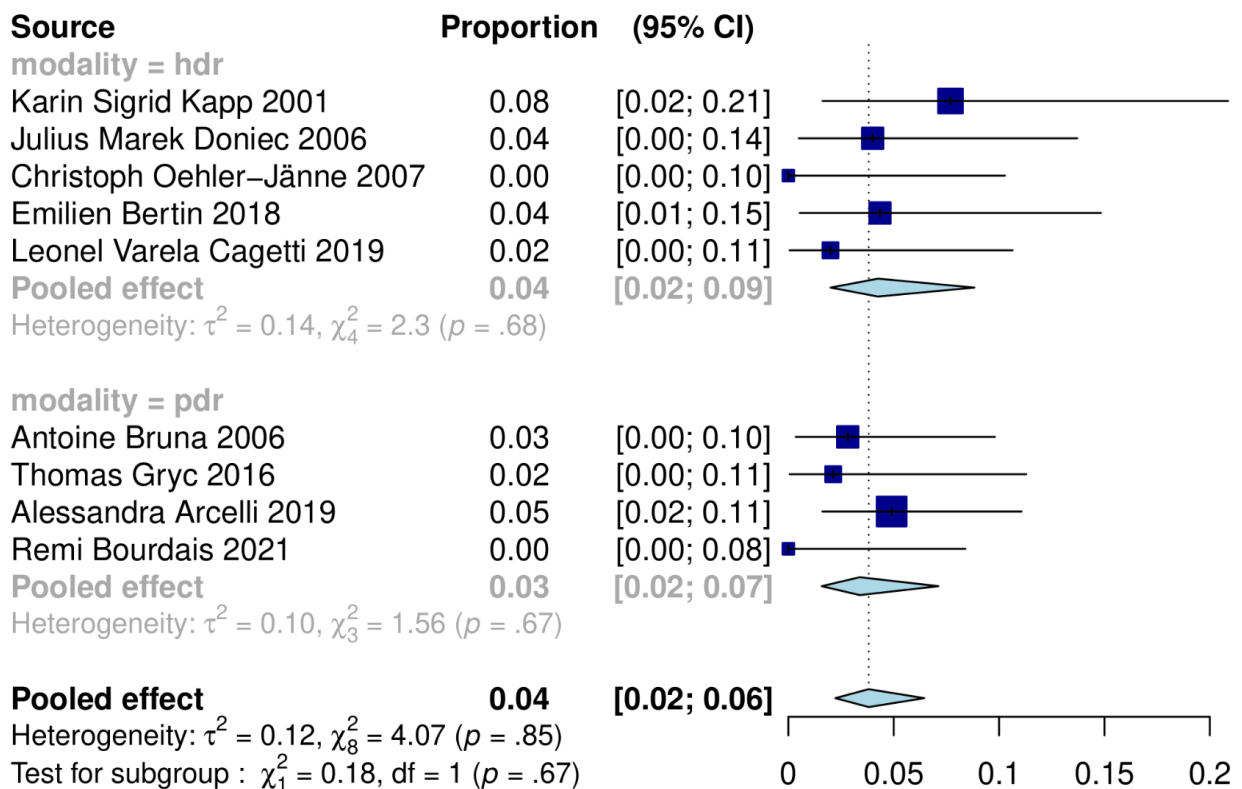


Figure 2.3. Forest plot of the proportion of colostomy related to toxicity.

HDR: high dose rate, PDR: pulsed dose rate, CI: confidence interval

2.2.5 Discussion

PDR and HDR brachytherapy are both excellent treatment modalities to boost residual disease and spare uninvolved parts of the anus in treatment of anal canal carcinoma. From a radiobiological point of view, the therapeutic ratio should theoretically be better for PDR brachytherapy and to reach the same local control probability, HDR should lead to more frequent and/or severe toxicities than PDR (15). Clinical data however do not confirm this hypothesis and there is growing evidence that both PDR and HDR-brachytherapy provided excellent clinical outcomes, if properly applied. In a recent pooled analysis, limited toxicity and excellent local control with HDR brachytherapy in combination with external radiotherapy and chemotherapy was found(161).

The basic premise to design this meta-analysis was to gather high-quality studies reporting the treatment outcomes. Guided by this assumption, we included only studies with more than 20 patients by brachytherapy modalities (e.g. HDR or PDR) and with at least 24 months of median follow-up time. Using these criteria, we identified nine uncontrolled studies reporting on retrospective data. To date, this is the only meta-analysis evaluating the toxicities and treatment outcomes according to brachytherapy modality in anal canal cancer. In analyzed papers there were no significant differences between brachytherapy modalities regarding the rate of toxicity-related colostomy or pelvic toxicity grade 3 or more. Also the results show excellent local control and toxicity data as compared to EBRT series. For T1-T2 tumors, both HDR and PDR-brachytherapy use, yield to high local control rate and low morbidity. We observed that patients treated with PDR had significant more advanced tumors (T3/T4 and/or cN + tumors) and longer follow-up. Secondly, patients treated with PDR had more aggressive treatment as they were more likely to receive higher brachytherapy dose and concurrent chemotherapy. In this meta-analysis, patients had more advanced tumors in the PDR group, but the survival results did not significantly differ from those in the HDR group. This observation is in accordance with tumor control probability models suggesting that lower doses may be sufficient for small tumors such as T1-T2, while higher doses may be required for more advanced tumors(162,163). To date, regarding evidence-based medicine the optimal total dose including the boost varies between physical doses of 50.4 Gy (ACT II trial) and 55-59 Gy for T3-T4 or node-positive

(RTOG 98–11 trial).(164,165) European Society of Medical Oncology (ESMO) guidelines recommended total doses of at least 45–50 Gy for T1–2 N0 while higher doses may be required for more advanced or poor responding tumors, using boost doses to the primary tumor ranging from 15 to 25 Gy EQD2. In the studies included in the meta-analysis, all the HDR studies reported a median brachytherapy dose lower than 15 Gy EQD2 while in all PDR studies the median brachytherapy dose was higher than 15 Gy EQD2. Thus, while the boost of 15 Gy or higher provided with PDR appeared safe and effective, additional clinical data are needed to refine the optimal fractionation and dose for HDR-brachytherapy treatments in advanced cases.

This analysis is subject to the inherent selection bias of the retrospective studies, but given the rarity of centers performing brachytherapy boost, randomized data will likely never be acquired. There were discrepancies in the quality, size, and selection processes within the studies included in the meta-analysis. Most of the studies didn't provide details on toxicities, however every study reported the number of toxicity-related colostomy. Only seven studies reported the late pelvic toxicity grade 3 or more. Late toxicities Grade 2 or more were not detailed in most of the studies. This is why we chose toxicity-related colostomy as the main criteria. Regarding local control, data extraction from Kaplan Meier curve was available for all but one study and overall survival for all studies. There was also the possibility of a selection bias. The most evident was the tumor stage that was more advanced in the PDR group. Because HDR brachytherapy was applied more recently than PDR-brachytherapy, there are fewer published data, especially for advanced tumors. Moreover, the study published by Gryc et al. included patients selected for poor tumor responses after EBRT, but despite this selection bias, survival outcomes and toxicities in this study were in the range of the other PDR studies.

Another limitation is the low number of studies included in the meta-analysis, which didn't allow us to adjust for confounding factors by performing a meta-regression analysis. As well the minimum sample size of the selected studies is low therefore the bias caused by sampling error should be strongly considered. In addition, there is in the literature heterogeneity in dose reporting among series and in next studies, a reproducible target and appropriate dose reporting concept will be mandatory for accurate dose/response and dose finding analysis. There is scarce data on modern approaches involving the possibility to include magnetic resonance

imaging (MRI) based target concepts in brachytherapy for anal canal cancer, as well as transrectal ultrasound guided implantations with MRI-compatible applicators and careful dose optimization based on the ground rules of the Paris system.

To date, dose/effect relationships to guide treatment planning and optimization are lacking. Beyond the question of comparing PDR and HDR, further studies are warranted to better identify dose/response effects and therefore guide total dose and fractionation choice. The observation that higher levels of EQD2 doses were used with PDR brachytherapy may question the clinical relevance of the linear quadratic model to provide reliable comparison tools for the biological effect in all clinical scenarios. In a retrospective series of patients treated for lip cancer with brachytherapy, equieffectiveness was shown with LDR brachytherapy at 70 Gy EQD2, and HDR brachytherapy schemes delivering 45 Gy in 9 fractions of 5 Gy (EQD2 = 56.3 Gy).⁽¹⁶⁶⁾ These observations suggest that choice of fractionation should rely on published clinical data, not only on EQD2 calculation derived from the linear quadratic model. A limitation is the use of 1.5 h half time of repair as a standard value. In case of lower half time of repair the calculated PDR EQD2 values would be lower, which could explain such observed equieffectiveness. Lower EQD2 values explaining tumor control of PDR would not directly lead to a substantially reduced therapeutic window, as the half time of repair could be also lower for late reactions in OARs.

2.2.6 Conclusion

In conclusion, it is not possible to draw conclusions on the superiority of one brachytherapy modality over another, because of the study design and limitations highlighted above. Both PDR and HDR brachytherapy modalities provided a high efficacy for boosting anal canal cancer, with good profile of tolerance, but using significant different dose levels according to the EQD2 model (mean brachytherapy EQD2 dose 11.9 Gy with HDR brachytherapy vs 19.5 Gy with PDR brachytherapy, $p < 0.001$) and with PDR brachytherapy more frequently used for advanced cases (T3/4N + tumors). These higher doses were not associated with higher incidence of late side effects in reported retrospective analyses. For now, PDR brachytherapy still has a crucial role to increase the dose in advanced cases, in parallel with ongoing developments to better determine the place of HDR for large tumors and with dose escalation strategies.

2.3 Summary and outlook

Although the superiority of PDR brachytherapy over HDR brachytherapy has yet to be confirmed, our study in anal canal cancer patients provides some important insights into the potential clinical benefits of PDR.

Specifically, we found that PDR brachytherapy allowed for the delivery of significantly higher radiation doses than is typical with HDR brachytherapy.

Furthermore, our study showed that using PDR brachytherapy for dose escalation above the usual limits of HDR brachytherapy can result in similar levels of local control for patients with very locally advanced tumors as for those with early stage tumors. This suggests that PDR may be a valuable option for patients with advanced disease who may not be candidates for other treatments.

Importantly, we also found that the use of PDR brachytherapy with significantly higher doses than with HDR brachytherapy did not result in a higher incidence of late side effects in reported analyses.

These findings taken together support the potential benefits of PDR brachytherapy and are consistent with radiobiological models that predict an improved therapeutic window with PDR.

3 Exploring the theoretical potential of PDR in LACC patients

3.1 Background

In the first section of this work, we delved into the radiobiological foundations of brachytherapy, focusing on the dose/rate effect, which has been the most extensively researched radiobiological parameter within the context of brachytherapy treatments. We also acknowledged the limited data available supporting the influence of other radiobiological factors underlying brachytherapy's effects. Through the review of preclinical studies, we confirmed the theoretical radiobiological potential of PDR brachytherapy over HDR brachytherapy. Moreover, we discussed the biological models based on the linear quadratic model and the incomplete repair model, which offer estimations of the optimal settings for brachytherapy modalities, as well as predictive models that evaluate the probability of normal tissue complications and local tumor control.

In the second section, we presented a meta-analysis of patients with anal canal cancer, which aimed to shed light on the potential clinical benefits of PDR brachytherapy. While not definitively confirming the superiority of PDR brachytherapy over HDR, the meta-analysis revealed important insights, such as the ability to deliver higher radiation doses and achieve similar levels of local control for both advanced and early-stage tumors through dose escalation, without an increase in side effects. These findings supported the potential clinical advantages of PDR brachytherapy and aligned with radiobiological models predicting an improved therapeutic window with PDR.

Building on the foundations of the previous sections, in the third section, we aimed to estimate the proportion of patients with LACC who could potentially benefit from PDR brachytherapy over HDR brachytherapy, and to assess the expected theoretical clinical impact. To accomplish this, we employed the linear quadratic model, which played a significant role in our understanding of the radiobiological basis of brachytherapy treatments and helped us identify the most appropriate brachytherapy modality for specific situations.

By estimating the subgroup of patients who might benefit from PDR over HDR, we aimed to provide valuable information that could inform future clinical decisions

and research efforts. This section also sought to evaluate the potential limitations of this approach, considering the insufficient knowledge regarding the parameters that should be applied for EQD2 estimation.

3.1 Radiobiological optimization comparison between pulse-dose-rate and high-dose-rate brachytherapy in patients with locally advanced cervical cancer

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3.1.1 ABSTRACT

Purpose : Only scarce data are available on the possibility to include radiobiological optimization as part of the dosimetric process in cervical cancer treated with brachytherapy (BT). We compared dosimetric outcomes of pulse-dose-rate (PDR) and high-dose-rate (HDR)-BT, according to linear-quadratic model.

Methods And Materials : Three-dimensional dosimetric data of 10 consecutive patients with cervical cancer undergoing intracavitary image-guided adaptive PDR-BT after external beam radiation therapy were examined. A new HDR plan was generated for each patient using the same method as for the PDR plan. The procedure was intended to achieve the same D_{90} high-risk clinical target volume with HDR as with PDR planning after conversion into dose equivalent per 2 Gy fractions (EQD2) following linear-quadratic model. Plans were compared for dosimetric variables.

Results : As per study's methodology, the D_{90} high-risk clinical target volume was strictly identical between PDR and HDR plans: 91.0 Gy (interquartile: 86.0-94.6 Gy). The median D_{98} intermediate-risk clinical target volume was 62.9 Gy_{EQD2} with HDR vs. 65.0 Gy_{EQD2} with PDR ($p < 0.001$). The median bladder D_{2cc} was 65.6 Gy EQD2 with HDR, vs. 62 Gy_{EQD2} with PDR ($p = 0.004$). Doses to the rectum, sigmoid, and small bowel were higher with HDR plans with a median D_{2cc} of 55.6 Gy_{EQD2} (vs. 55.1 Gy_{EQD2}, $p = 0.027$), 67.2 Gy_{EQD2} (vs. 64.7 Gy_{EQD2}, $p = 0.002$), and 69.4 Gy_{EQD2} (vs. 66.8 Gy_{EQD2}, $p = 0.014$), respectively. For organs at risk (OARs), the effect of radiobiological weighting depended on the dose delivered. When OARs BT contribution to D_{2cc} doses was < 20 Gy_{EQD2}, both BT modalities were equivalent. OARs EQD2 doses were all higher with HDR when BT contribution to D_{2cc} was ≥ 20 Gy_{EQD2}.

Conclusion : Both BT modalities provided satisfactory target volume coverage with a slightly higher value with the HDR technique for OARs D_{2cc} while intermediate-risk clinical target volume received higher dose in the PDR plan. The radiobiological benefit of PDR over HDR was predominant when BT contribution dose to OARs was > 20 Gy.

Keywords : Linear-quadratic model, Pulse-dose-rate brachytherapy, High-dose-rate brachytherapy, Cervical cancer, Radiobiological effect

3.1.2 Introduction

Intracavitary brachytherapy delivered after concurrent chemoradiation plays a major role in the treatment of locally advanced cervical cancer and represents the standard of care.(167) To date, the diverse treatment approaches derived from historical brachytherapy schools (e.g., Manchester, Paris, Stockholm) still dominate the basic dosimetric principles. In addition, many new developments such as new applicators, image-guided adaptive brachytherapy, and the HDR and PDR remote control afterloading systems have contributed further to increase optimization capabilities.

HDR brachytherapy was initiated in the late 1950s with ^{60}Co and has been increasingly used for the treatment of LACC. Currently, HDR is widely used instead of LDR and has substantial advantages in terms of physics properties and convenience (dose optimization, radiation safety, and short treatment time). Radiobiologically, LDR is considered advantageous over HDR in terms of late tissue effects, although not reflected in randomized trials reporting that probabilities of local control and overall survival were similar for LDR and HDR treatments.(91,92,168,169) However, those trials have been criticized for a number of methodologic limitations (patients and tumors heterogeneity, utilization of different radiation techniques, followup limitations).(170) In a randomized comparison of two LDRs (0.4 vs. 0.8 Gy/h), prevalence of complications over time was increased in the HDR group, without difference in terms of local control, confirming that dose rate had a differential impact between tumor and normal tissue response.(171)

PDR brachytherapy was developed in the 1990s, theoretically combining physical advantages of HDR and radiobiological advantages of LDR brachytherapy. With PDR brachytherapy, instead of delivering the dose continuously as in LDR, a series of continuous hourly pulses is delivered, few minutes each hour. Typically, the overall dose and treatment time are the same as the corresponding LDR schedule. PDR compared to LDR has many specific advantages such as isodose optimization capability, better therapeutic ratio attributed to multiple fractionation regimens leading to cell cycle redistribution, and excellent radiation protection.(31,95) From a logistic point of view, the main disadvantage of the PDR compared with HDR is the need for a dedicated hospital room equipped with a remote afterloading system. Therefore,

the possible number of brachytherapy procedures that can be performed daily is limited. On the other hand, the number of applications is reduced. To date, only scarce data are available on the possibility to include radiobiological optimization as part of the dosimetric process, although this strategy has been pointed out in the last International Commission on Radiation Units and Measurements guidelines dedicated to brachytherapy. The aim of this study was to explore the radiobiological impact of brachytherapy modality on dosimetric outcomes, according to linear-quadratic model.

3.1.3 Methods

Patient population

Clinical and dosimetric data of 10 consecutive patients receiving intracavitary image-guided adaptive brachytherapy after pelvic EBRT and concomitant chemotherapy in 2016 for an LACC were examined. Only patients with N0 disease after an exhaustive pretreatment workup were included to overcome the issue of potential contribution of simultaneous lymph node boosts. The EBRT radiation procedure has been reported in detail before.(172) Briefly, all patients received a pelvic EBRT, with a normal fractionation delivering 45 Gy in 25 daily fractions over 5 weeks, delivered through IMRT (Helical TomoTherapy, Accuray, CA).

Linear quadratic model

For radiobiological weighting, the linear quadratic model for incomplete repair was used.(107) As an input for the model, the GEC ESTRO recommendations suggest a uniform value of α/β ratio = 10 Gy for tumor and clinical target volume and α/β ratio = 3 Gy for all OARs. The modeling of PDR requires a value for the $T_{1/2}$, although $T_{1/2}$ is not as consolidated as the previous biological parameters, the GEC ESTRO refers that 1.5 h is the “best estimate” for this parameter; therefore, this value was used for all tissues involved. With these parameters, the EQD2 was calculated. Cumulative dose volume histograms were generated, by adding the contribution of EBRT (45 Gy in 25 fractions) with that of brachytherapy.

PDR brachytherapy procedure

The implantation technique description is available in a previous publication.(172) After the implantation, based on the vaginal mold applicator technique, a pelvic MRI was acquired, with T2 sagittal, axial, and coronal sequences, which were transferred to BrachyVision (Varian Medical Systems, Palo Alto) platforms to perform contouring of the gross target volume, high-risk clinical target volume (CTV_{HR}), intermediate-risk clinical target volume (CTV_{IR}), and OARs according to European recommendations from the GEC ESTRO. The planning process started with an activation of the dwell positions in regard to the CTV_{IR} , and a standard physical dose of 15 Gy in 30 pulses of 0.5 Gy (corresponding to an EQD2 dose of 15 Gy according to linear quadratic model) was prescribed and normalized to

Point A. The optimization process was aimed at achieving the following planning objectives : $D_{90} \text{ CTV}_{\text{HR}} \geq 85 \text{ Gy}_{\text{EQD2}}$, $D_{98} \text{ CTV}_{\text{IR}} \geq 60 \text{ Gy}_{\text{EQD2}}$, D2cc of the bladder $\leq 85 \text{ Gy}_{\text{EQD2}}$, D2cc of the rectum and sigmoid $\leq 75 \text{ Gy}_{\text{EQD2}}$. Dwell times and positions were adjusted manually by the same pair of radiation oncologist and physicist, in an iterative way until dose volume histograms constraints were fulfilled as best as possible.

Conversion to HDR planning treatment

A new ^{192}I HDR dosimetry was performed for each patient using the same image set than for the PDR plan. In the same way, the treatment planning process started with an activation of the same dwell positions as in the PDR planning treatment. A standard physical dose of 13.48 Gy in four fractions of 3.37 Gy (corresponding to an EQD2 dose of $15 \text{ Gy}_{\text{EQD2}}$ according to linear quadratic model) was prescribed and normalized to point A. Then, the dwell time for each dwell position was optimized manually in an iterative way following the same pattern as for the PDR optimization. The procedure aimed to reach the same coverage of $D_{90} \text{ CTV}_{\text{HR}}$ than in the PDR plan with a margin of error $\leq 0.1 \text{ Gy}$.

Data extraction and statistics

PDR and HDR plans were compared using dosimetric variables for the clinical target volume and OARs. Clinical target volume metrics included $D_{90} \text{ CTV}_{\text{HR}}$ (control variable) and $D_{98} \text{ CTV}_{\text{IR}}$. OAR metrics included D2cc of the bladder, rectum, sigmoid, and small bowel. Differences in dosimetric variables were evaluated for statistical significance ($p < 0.05$) using the twotailed Student's paired t-test. Before application of the Student's t-test, the data were verified to be normally distributed using a Shapiro-Wilk test. Finally, the double ratio $\text{EQD2}_{\text{rectum}}/\text{EQD2}_{\text{CTVHR}}$ (derived from the $\text{BED}_{\text{NT}}/\text{BED}_{\text{TUM}}$ ratio described by Sminia et al.) was applied as a function of the overall brachytherapy duration in PDR plan, which is directly correlated to the number of pulses and inversely correlated to the dose per pulse.(173) This double ratio represents the therapeutic ratio of HDR relative to PDR depending on the dose per pulse applied in the PDR plan :

$$\text{HDR/PDR therapeutic ratio} = \frac{D_{2cc\text{rectum EQD2}}(\text{HDR})/D_{2cc\text{rectum EQD2}}(\text{PDR})}{D_{90\text{CTV}_{HR}\text{EQD2}}(\text{HDR})/D_{90\text{CTV}_{HR}\text{EQD2}}(\text{PDR})}$$

Data management and statistical analyses were performed using R 3.4.1 software (The R Foundation for Statistical Computing Platform, Vienna, Austria).

3.1.4 Results

Patients and EBRT dose contribution

Data from 10 patients treated with endocavitary BT only were analyzed. Tumor Fédération Internationale de Gynecologie et d'Obstetrique (FIGO) stages were as follows: two stage IB2, six stage IIB, one stage IIIA, and one stage IIIB. Tumor involved the lower third of vagina in two patients; the middle and the upper third of the vagina were involved in two patients. Regarding pelvic EBRT, for all patients, dose delivered to the planning target volume was 45 Gy with dose per fraction of 1.8 Gy. Following International Commission on Radiation Units and Measurements guidelines, the contribution of EBRT to clinical target volume and OAR metrics assessed in brachytherapy plan were therefore considered equal to 44.3 Gy_{EQD2} and 43.2 Gy_{EQD2}, respectively (all doses in 2-Gy equivalents, applying the linear quadratic model with a α/β ratio of 10 for target volumes and three for OARs). Dosimetric data for both treatment modalities are listed in **Table 3.1.1**.

Pulse-dose rate brachytherapy

Median number of pulses was 50 (interquartile range [IQR], 47e53). The aforementioned planning aims for CTVHR were reached for seven patients. Among the three others, two were very close with a D90 CTVHR of 84.4 GyEQD2 and 84.0 GyEQD2, respectively. The median D90 CTVHR and D98 CTVIR were 91.0 GyEQD2 (IQR, 86.0e 94.6 GyEQD2) and 65.0 GyEQD2 (IQR, 62.9e65.5 GyEQD2), respectively. Planning aims for OARs were reached for every patient. The median D2cc of the bladder, rectum, sigmoid, and small bowel were 62 GyEQD2 (IQR, 58.8e70.2 GyEQD2), 55.1 GyEQD2 (IQR, 54.3e55.6 GyEQD2), 64.7 GyEQD2 (IQR, 56.0e67.7 GyEQD2), and 66.8 GyEQD2 (IQR, 59.2e75.9 GyEQD2), respectively.

	PDR BT	HDR BT	P-value
Target volume			
D ₉₀ CTV _{HR} (Gy)	91.0 (86.0-94.6)	91.0 (86.0-94.6)	NA
D ₉₈ CTV _{IR} (Gy)	65.2 (62.9-65.5)	62.9 (60.9-63.7)	< 0.001
Organs at risk			
D2cc Bladder (Gy)	62.9 (58.8-70.2)	65.6 (59.7-76.3)	0.004
D2cc Rectum (Gy)	55.1 (54.3-55.6)	55.6 (54.5-56.3)	0.027
D2cc sigmoid (Gy)	64.7 (56.0-67.7)	67.2 (56.7-71.9)	0.002
D2cc small bowel (Gy)	66.8 (59.2-75.9)	69.4 (59.8-85.5)	0.014

BT = brachytherapy; HDR = high-dose rate; LDR = low-dose rate; PDR = pulsed-dose rate

Table 3.1.1. Dosimetry of targets volume and organs at risk (median with interquartile ranges)

High-dose rate brachytherapy

According to the study's methodology, the D₉₀ CTV_{HR} coverage was strictly identical to that obtained with the PDR plan. The CTV_{IR} coverage was lower with HDR brachytherapy for all patients. The median D₉₈ CTV_{IR} was 62.9 Gy_{EQD2} (vs. 65.0 Gy_{EQD2} with PDR, p < 0.001). Conversely, dose to the bladder was increased with HDR brachytherapy for all patients. The median bladder D2cc was 65.6 Gy_{EQD2} (vs. 62 Gy_{EQD2}, p = 0.004). Doses to the rectum, sigmoid, and small bowel were higher in 7, 9, and 8 cases with a median D2cc of 55.6 Gy_{EQD2} (vs. 55.1 Gy_{EQD2}, p = 0.027), 67.2 Gy_{EQD2} (vs. 64.7 Gy_{EQD2}, p = 0.002), and 69.4 Gy_{EQD2} (vs. 66.8 Gy_{EQD2}, p = 0.014), respectively.

Linear-quadratic model effect

As shown in **Figure 3.1.1**, the impact of the linear quadratic model was different according to the dose level and the α/β ratio value considered.

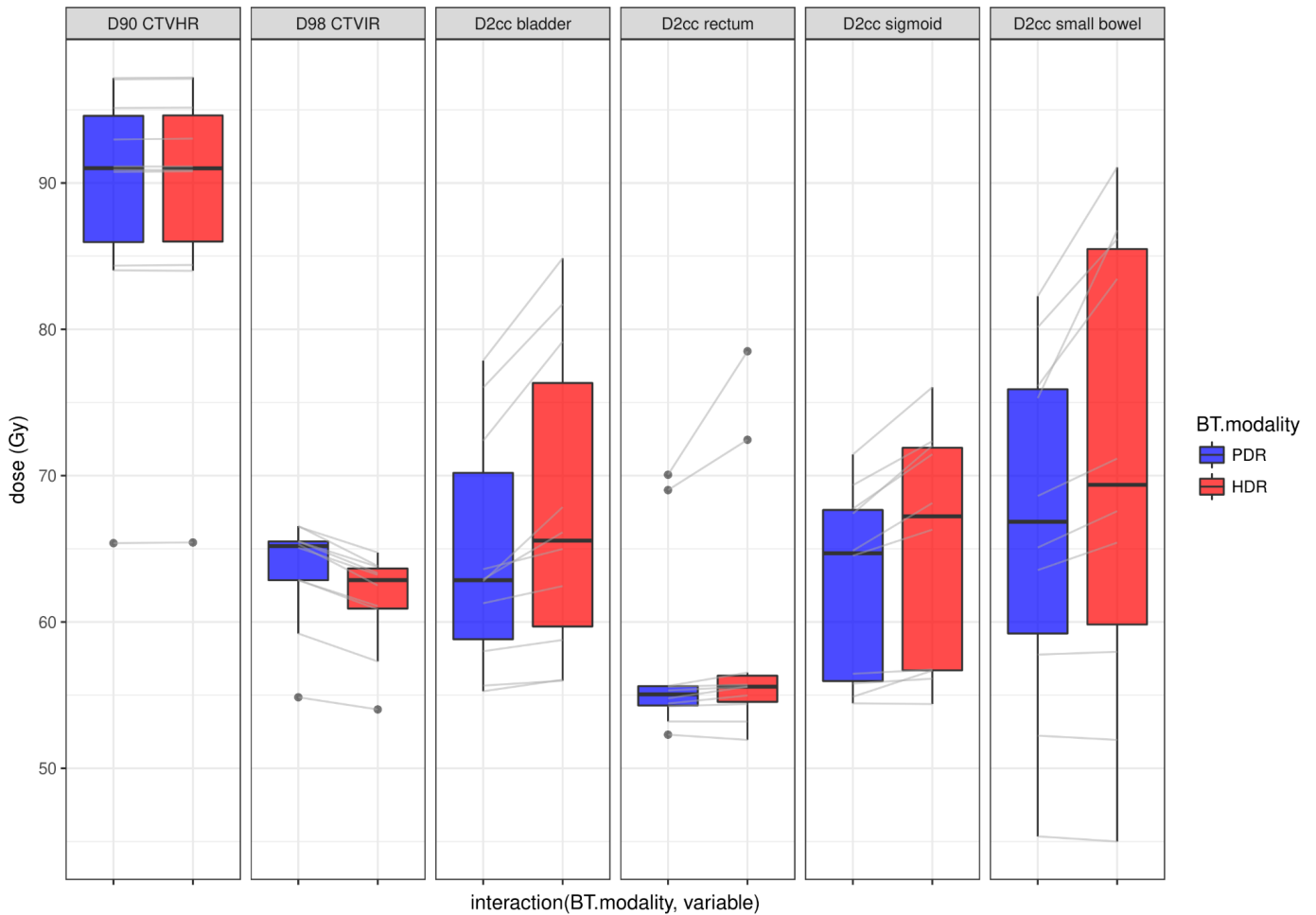


Figure 3.1.1. Paired box plot of target and normal tissue metrics following brachytherapy modality. BT = brachytherapy, HDR = high-dose-rate, PDR = pulsed-dose-rate.

Regarding the target volumes (α/β ratio = 10 Gy), at the same physical dose, EQD2 D_{90} CTV_{HR} was higher for HDR dosimetry, as compared with PDR. To adjust both plans on radiobiologically weighted D_{90} CTV_{HR}, the HDR physical dose had to be decreased. Therefore, the physical dose delivered to D_{98} CTV_{IR} was also decreased in the same range. Consequently, for two plans achieving the same EQD2 D_{90} CTV_{HR}, the EQD2 D_{98} CTV_{IR} was lower for HDR plan, as a result of radiobiological weighting in this area receiving lower doses. This effect is shown in **Figure 3.1.2**.

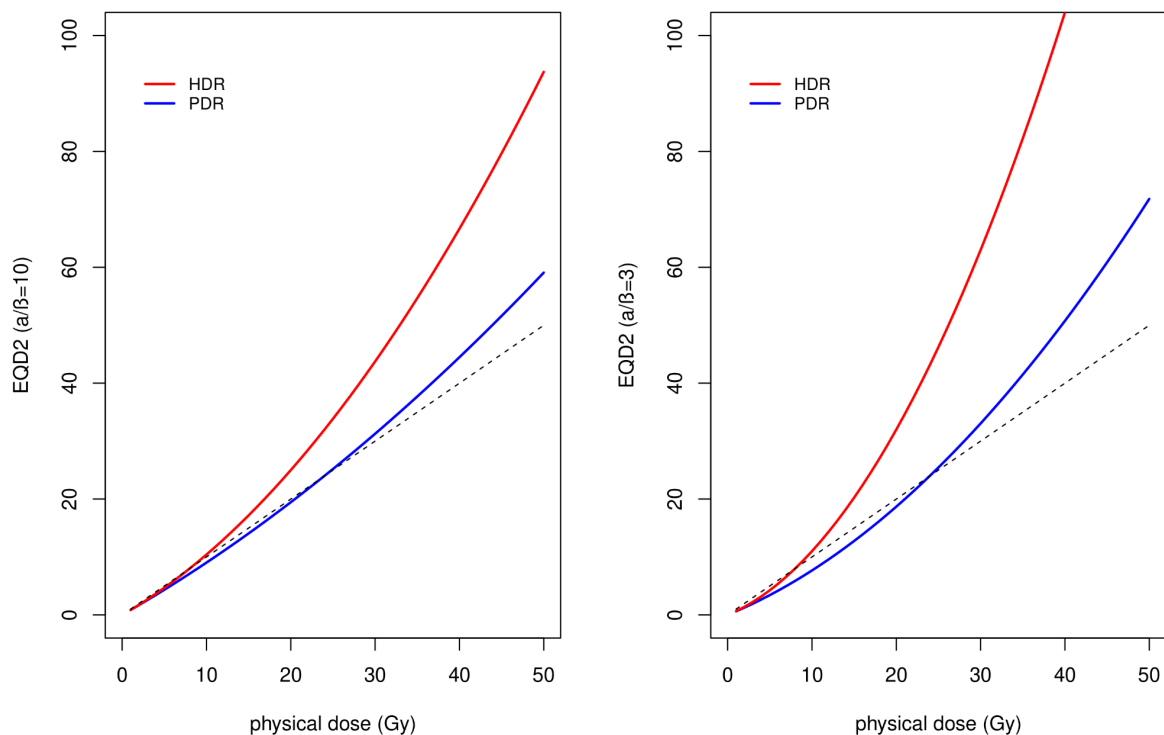


Figure 3.1.2. Linear-quadratic model for organs at risk (α/β ratio) and target volumes (α/β ratio = 10Gy). HDR = high-dose-rate; PDR = pulsed-dose-rate.

Regarding the OAR (a/b ratio = 3 Gy), lowering the HDR physical dose to adjust both plans on radiobiologically weighted D_{90} CTV_{HR} led to decrease of the EQD2, and the extent of decrease depended on the brachytherapy contribution. When the dose contribution of brachytherapy was very low, the effect of radiobiological weighting was also low, leading to EQD2 D2cc being almost equivalent for PDR and HDR dosimetry. However, when brachytherapy contribution increased, the decrease of physical dose caused by the adjustment on D_{90} CTV_{HR} did not counterbalance the radiobiological effect for HDR OARs. Thus, the EQD2 D2cc doses calculated for OARs were always higher for HDR plan (**Figure 3.1.2**). Although no firm dose threshold could be identified, the effect of radiobiological weighting became obvious for brachytherapy doses $> 20 \text{ Gy}_{EQD2}$.

The interaction between dose level and the linear quadratic model is summarized in **Figure 3.1.3**. Converting PDR dosimetry to HDR had quite a similar impact on EQD2 CTV_{IR} for the range of doses reported in our population, decreasing

the dose uniformly for all patients. For OARs, the effect of radiobiological weighting depended on the dose delivered. For implants in which brachytherapy contribution was low, schematically $D_{2cc} < 20 \text{ Gy}_{\text{EQD2}}$, there was equivalence between both brachytherapy modalities. However, when OARs D_{2cc} doses were $> 20 \text{ Gy}_{\text{EQD2}}$, conversion of PDR to HDR led to systematically increase OAR doses.

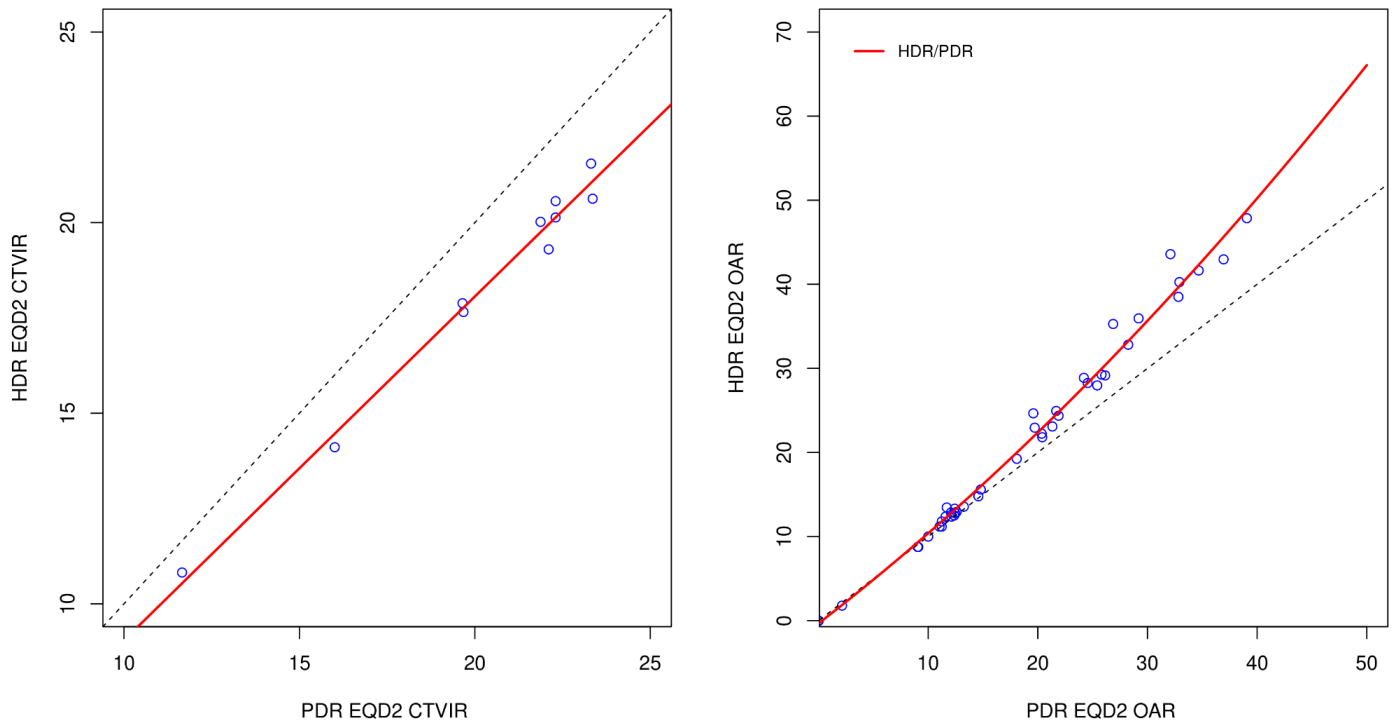


Figure 3.1.3. Comparison of 2 Gy equivalent dose (EQD2) between high-dose-rate and pulse-dose-rate brachytherapy. Each point represents a dosimetric variable for one patient. The abscissa represents the EQD2 of the PDR plan, whereas the ordinate represents the EQD2 of the HDR plan. When the point is above the dashed line, this means that the dose EQD2 is higher in the HDR plan. CTVIR : intermediate-risk clinical target volume, HDR : high-dose-rate, OAR : organ at risk, PDR : pulsed-dose-rate.

Radiobiological optimization

Figure 3.1.4 shows the HDR/PDR therapeutic ratio ($[\text{EQD2}_{\text{HDR}}/\text{EQD2}_{\text{PDR}}]D_{2cc} \text{ rectum}/[\text{EQD2}_{\text{HDR}}/\text{EQD2}_{\text{PDR}}]D_{90} \text{ CTV}_{\text{HR}}$) as a function of the dose per pulse in PDR treatments for an unchanged prescribed dose of 15 Gy. For illustrative purposes, only four representative patients were plotted, that is, the patient with the highest rectal dose, the one with the lowest rectal dose, and two with intermediate physical D_{2cc}

doses. We observed that the impact of modifying dose per pulse in PDR was dependent on the level of dose. Schematically, when rectal physical D2cc was low, lowering the dose per pulse in PDR (increasing total number of pulses) was not associated with an expected therapeutic gain. Contrariwise, the differential effect associated with dose per pulse reduction was significant when the physical dose level increased. This observation was particularly substantial when PDR physical dose to the rectal D2cc exceeded 20 Gy.

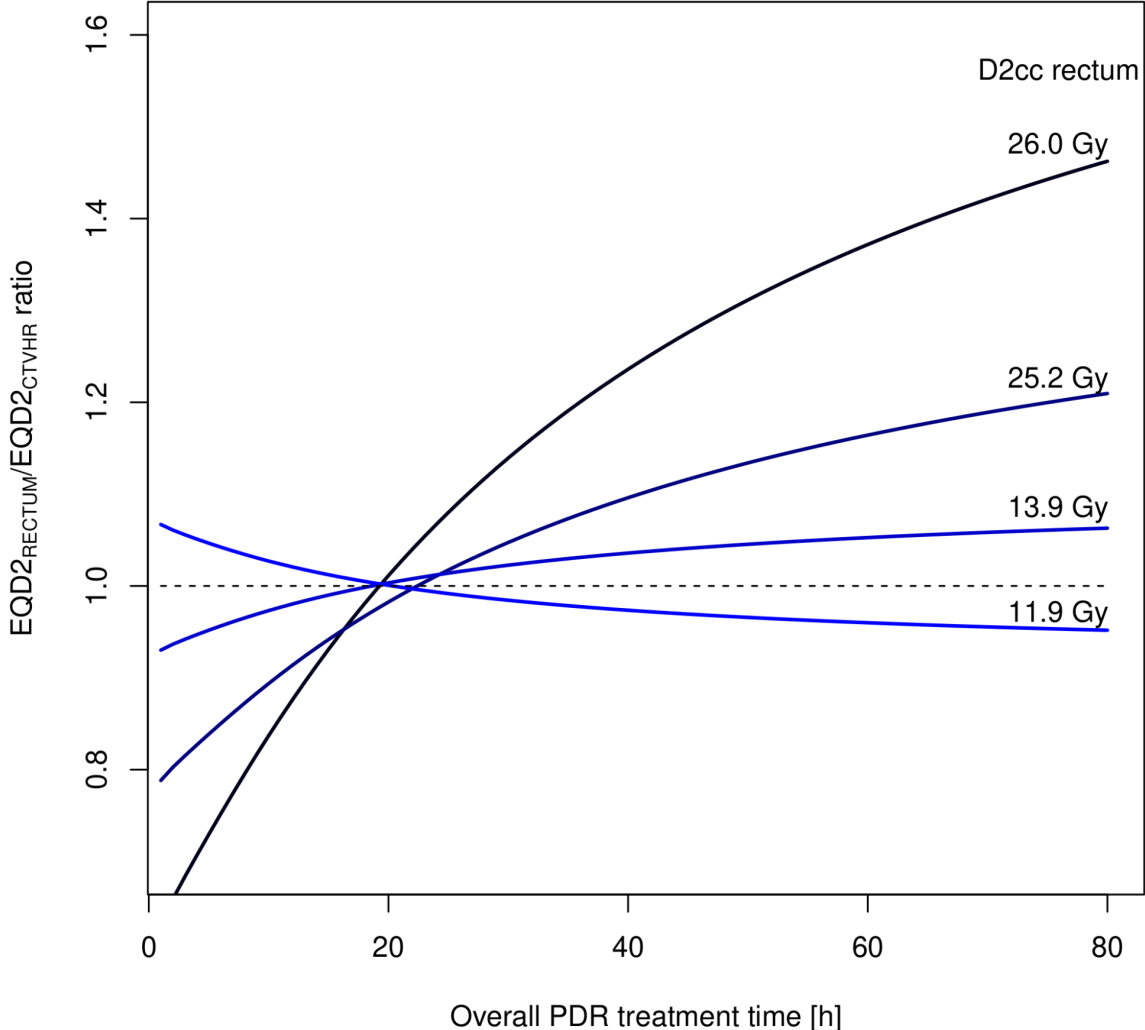


Figure 3.1.4. Therapeutic ratio of HDR relative to PDR, according to total number of hourly pulses. When the ratio is superior to 1 (above the dashed line), PDR allowed a better therapeutic ratio over HDR. D2cc rectum indicates the physical dose to the rectum in the initial PDR plan. HDR : high-dose rate; PDR : pulsed-dose rate.

3.1.5 Discussion

Most studies comparing radiobiology of HDR vs. LDR found a better therapeutic ratio in favor of LDR.(86–88) Although there is a theoretical risk of increased complications with HDR compared with LDR, this has not been seen in properly randomized trials or meta-analysis.(89–92) The main explanation is that HDR brachytherapy offers the possibility to optimize by adjusting dwell times and positions, counterbalancing its radiobiological disadvantage. PDR brachytherapy offers the possibility to combine the radiobiological advantage of LDR and isodose optimization, as allowed by HDR brachytherapy. Indeed, it was published from radiobiological studies that PDR appeared to be functionally equivalent to a continuous irradiation regimen, for both early and late effects.(106) However, to our knowledge, PDR brachytherapy and HDR brachytherapy have not been compared properly in radiobiological studies. The theoretical benefit of PDR, if any, should theoretically vary according to several factors such as dose rate or tissue's characteristics ($T_{1/2}$, α/β ratio).(37,106)

In the scientific literature, there is very little data available comparing PDR and HDR brachytherapy. The only randomized prospective study was conducted by Kumar et al. on 37 patients with locally advanced carcinoma of the cervix.(95) Patients were randomized to receive either HDR (7 Gy each in three fractions, repeated weekly) or PDR (70 cGy hourly pulses for 39 h, total 27 Gy) brachytherapy after EBRT. Toxicity rate did not differ significantly in this low-power study although a trend in favor of PDR was observed. In the PDR arm, the rate of late rectal toxicity grade ≥ 2 was 21.1% (vs. 16.7% in HDR) and 0% (vs. 10.5%) for grade ≥ 3 , the rate of late bladder toxicities grade ≥ 2 was 0% (vs. 10.5%), and the rate of late vaginal toxicities grade ≥ 2 was 5.6% (vs. 15.8%). The 4-year disease-free survival rate was 67.1% vs. 71.8% ($p = 0.195$).

Enrollment of patients in large clinical trials comparing both PDR and HDR brachytherapy does not seem feasible or even relevant. The prospective EMBRACE study has included approximately one-third of patients treated with PDR brachytherapy. This large study may provide further insights into the dose-rate effect in patients treated according to modern standards of intracavitary image-guided adaptive brachytherapy based on dose optimization. However, neither large

randomized study nor dosimetric comparison of both brachytherapy modalities exists, and it is therefore still difficult to anticipate which patients may benefit from PDR or from HDR. Our findings suggest a slight difference between HDR and PDR when plans were adjusted on $D_{90} \text{CTV}_{\text{HR}}$. Both techniques provided acceptable target volume coverage with a slightly higher value with the HDR technique for OAR D2cc while CTV_{IR} received higher dose in the PDR plan. The theoretical radiobiological benefit of PDR over HDR became predominant when doses to OARs were superior to $20 \text{Gy}_{\text{EQD2}}$, although no firm dose threshold could be identified. We found that above this range of dose, the higher the dose, the greater the difference between both brachytherapy modalities (**Figure 3.1.3**). Similarly, the effect of adjusting both plans on radiobiologically weighted $D_{90} \text{CTV}_{\text{HR}}$ led to clinically relevant differences in terms of bladder EQD2 D2cc but had only marginal effect in terms of rectal EQD2 D2cc, which is in line with the fact that higher physical doses were delivered to the bladder (**Figure 3.1.1**).

Although PDR use is decreasing worldwide, it is still being proposed in several large institutions, and its radiobiological advantages are consensual for treatment of highly sensitive area, such as anal canal, penile glans, vagina, oral mucosa, or in pediatrics indications.(3,97) The results of this study provide new insights to guide future study searching for patients with LACC who could benefit from PDR vs. HDR brachytherapy, notably those with significant exposure to OARs and those with large CTV_{IR} . Indeed, according to our results, most patients had an equivalent dosimetry regardless of the brachytherapy modality. The possibility to perform virtual preplanning for intracavitary image-guided adaptive brachytherapy applications has been reported in the literature.(14) A preselection of patients based on the expected contribution of brachytherapy to OARs and the CTV_{IR} might increase the chance to optimize the therapeutic effect in these patients through radiobiological optimization and to give centers having both brachytherapy modalities available the possibility to decide which treatment will be the most appropriate. Next step will be to anticipate which patients may benefit more from PDR than from HDR brachytherapy, if any, based not only on the expected OARs dose but also on tumor characteristics such as the size, the CTV_{HR} , or the expected contribution to lymph node dose.

Another issue addressed in this study was the possibility to adjust dose per pulse to modify the therapeutic ratio. In some institutions treating patients with PDR

brachytherapy, dose rate is corrected by decreasing the dose rate to the isodose prescription and increasing the total number of pulses to not exceed the limit of 0.6 Gy/h to the OARs.(172) It was hypothesized that going further in this process could be beneficial in terms of therapeutic index by allowing dose escalation based on radiobiological optimization. Our results suggest that this kind of radiobiological optimization is relevant to decrease relatively more EQD2 D2cc than the $D_{90} \text{CTV}_{\text{HR}}$, and this effect was the most significant at increasing physical OAR doses. Notably, the benefit of decreasing dose per pulse was particularly important when physical brachytherapy dose contribution to rectal D2cc was $> 20 \text{ Gy}$, which would lead to a total $D2\text{cc} > 63.2 \text{ Gy}_{\text{EQD2}}$ ($43.2 \text{ Gy}_{\text{EQD2}}$ EBRT + $20 \text{ Gy}_{\text{EQD2}}$ brachytherapy). As this is still quite a low D2cc dose, as compared with usual guidelines for OARs dose constraints of $70\text{-}75 \text{ Gy}_{\text{EQD2}}$, our results suggest that in some cases radiobiological optimization may be relevant to achieve dose escalation (**Figure 3.1.4**).

This study has some limitations. Direct comparison of different brachytherapy treatment plans is quite complicated because of the heterogeneity of dose parameters for EQD2 calculation used in publications and the lack of widely accepted optimization methodology. Although there are recommendations by professional societies, no consensus exists regarding optimal parameters in the setting of radiobiological model because no validation study on large prospective cohort exists. Thus, the EQD2 given by radiological models cannot be considered as perfectly accurate. Furthermore, only patients with N0 disease were included and therefore the contribution of simultaneous lymph node boosts to the total EQD2 dose remains to be investigated. Finally, the dosimetric results reported here may not be extrapolated identically for other applicators, or other loading patterns. However, it should be highlighted that in patients with large CTV_{HR} , the effect of radiobiological optimization might be still higher. In the EMBRACE 2 study, highly stringent dose constraints have been provided in terms of CTV_{HR} dose objectives and for OARs sparing (e.g., planning aim for rectal D2cc dose $< 65 \text{ Gy}_{\text{EQD2}}$).(174) In the most advanced tumors or in case of poor response, such stringent objectives will be achievable only by means of a more frequent use of interstitial implantations, which were shown to give more capabilities in terms of dose escalation, without exceeding OARs dose constraints.(175) Our study did not address the question of interstitial applications, and this is another limitation.

3.1.6 Conclusion

In conclusion, our data suggest that radiobiological optimization may have a substantial role as part of the optimization process in very advanced tumors, either by identifying patients who may be treated with PDR rather than with HDR brachytherapy or by giving the possibility to make dose escalation by adjustments of dose per pulse.

3.2 Redefining the Role of Pulsed-Dose-Rate Brachytherapy in Cervical Cancer Treatment using a Pre-Planned Approach

Authors : Pierre ANNEDE, Charlotte ROBERT, Sophie ESPENEL, Isabelle DUMAS, Cyrus CHARGARI

3.2.1 Abstract

Introduction : This study aimed to identify factors that can predict which locally advanced cervical cancer (LACC) patients are more likely to benefit from high-dose-rate (HDR) or pulsed-dose-rate (PDR) brachytherapy, and to estimate the differential effect expected between the two treatment modalities.

Methods : Fifty consecutive LACC patients treated with brachytherapy after external radiochemotherapy were included in the study. For each patient, multiple PDR plans with 20 to 70 pulses were compared to a four-fraction HDR preplan. A subset of patients who particularly benefited from the PDR modality was identified using preplan metrics and clinical variables. The clinical effect expected was quantified using a tumor control probability (TCP) model.

Results : PDR plans with 60 pulses were found to be the most effective in achieving the target clinical goal for $D_{90}CTV_{HR}$. CTV_{HR} volume $> 67.5cc$ and/or $D_{90}CTV_{HR}$ dose on the HDR preplan less than 31.1Gy was identified as the best indicator for selecting patients who are likely to experience a greater than 3% increase in TCP with the PDR plan. The selection process had an accuracy of 0.96, sensitivity of 0.88, and specificity of 0.98. Out of the 50 patients included in the study, eight (16%) were identified as benefiting from PDR over HDR, with a mean $D_{90}CTV_{HR}$ of 7Gy higher [95%CI (6.2-7.7), p -value <0.0001] and a mean TCP at 3 years of 4.8% higher [95% CI (3.5-6.1), p -value <0.0001] for the PDR plan compared to the HDR preplan. The potential benefit of PDR was found to be highly influenced by the choice of alpha/beta ratio and repair halftime.

Conclusion : The results suggest that only a small number of LACC patients may benefit from PDR over HDR. CTV_{HR} volume and preplan $D_{90}CTV_{HR}$ doses should be considered as promising factors in the selection of patients for PDR brachytherapy.

Keywords: cervical cancer, brachytherapy, radiation therapy, Pulse dose rate brachytherapy, High dose rate brachytherapy.

3.2.2 Introduction

Brachytherapy as a consolidation treatment following radiochemotherapy is a widely used radiation treatment for LACC. HDR and PDR techniques are both commonly employed. PDR has a potential radiobiological advantage over HDR due to the extended duration of irradiation, which allows for a more physiological repair of sublethal damage(176). However, the use of PDR has been limited in many centers due to logistical issues.

Recent advances in brachytherapy implantation techniques have led to improvements in the optimization of dose distribution, potentially narrowing the theoretical gap in efficacy between the two approaches (177). Moreover, previous dosimetric studies have suggested that the benefit of PDR may only be clinically relevant when OARs are exposed to high doses (15). To date, there is no clinical trial with enough power comparing HDR vs PDR in the era of image-guided brachytherapy and with application of a robust dose prescription protocol. Therefore, it can be difficult to determine which patients may benefit more from PDR or HDR.

The aim of this study was to define objective criteria to identify patients benefiting from pulsed irradiation, based on an HDR pre-planning approach, focusing specifically on patients with the most advanced tumors. The clinical effect expected was quantified using TCP models.

3.2.3 Methods

Data

Fifty consecutive patients treated for LACC with brachytherapy were included in the study. Patients were selected from the Gustave Roussy database between December 2018 and May 2020 (all patients had been treated with PDR brachytherapy, as per local standard protocol). This non-interventional dosimetric study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments.

Dosimetry process

For each patient, several dosimetry plans were performed using the Oncentra brachytherapy planning system (Elekta, Stockholm, Sweden), based on magnetic MRI acquired with an applicator in situ. A preplan using HDR with 4 fractions and seven experimental plans were created, including a HDR plan with 6 fractions and PDR plans with 20, 30, 40, 50, 60, and 70 hourly pulses.

For each plan, doses to targets and OARs were assessed using the linear quadratic model for EQD2 per fraction, following GEC-ESTRO guidelines. The α/β ratio was set to 10 Gy for the tumor and clinical target volume and to 3 Gy for all OARs involved in late complications. The modeling of PDR required a value for the $T_{1/2}$. The GEC-ESTRO recommends 1.5 h as the “best estimate” for this parameter; therefore, this value was used for all tissues involved. All PDR treatments were considered as hourly pulses of 20 minutes.

For each plan, the optimization process aimed to reach the following optimal clinical goals (calculated in EQD2): $D_{90} \text{ CTV}_{\text{HR}} \geq 90 \text{ Gy}$, minimal dose to 98% of the intermediate-risk clinical target volume ($D_{98} \text{ CTV}_{\text{IR}} \geq 60 \text{ Gy}$). D2cc of organs at risk were as follows: D2cc bladder $\leq 80 \text{ Gy}$, D2cc rectum $\leq 65 \text{ Gy}$, D2cc sigmoid $\leq 70 \text{ Gy}$, and D2cc small bowel $\leq 70 \text{ Gy}$. The mandatory dose constraints to OARs were D2cc bladder $\leq 90 \text{ Gy}$, a D2cc rectum $\leq 75 \text{ Gy}$, D2cc sigmoid $\leq 75 \text{ Gy}$, and D2cc Small bowel $\leq 75 \text{ Gy}$. These doses were chosen as limits for prescribed dose, as per EMBRACE II protocol.(178)

Data extraction and endpoints:

Dosimetric data and volumes were extracted from ".dvh" files using the "DVHmetrics" package from R studio 2022.07.2.(149,179) Implantation data such as the type of applicator and the number of interstitial needles were collected.

The primary endpoint was TCP at 3 years calculated using a formula whose parameters were extracted from published results of the retroEMBRACE study.(180) Secondary endpoints were: $D_{90} \text{CTV}_{\text{HR}}$, $D_{98} \text{CTV}_{\text{IR}}$, D2cc bladder, D2cc sigmoid, D2cc small bowel, and D2cc rectum.

Selection of the best experimental brachytherapy modality:

PDR and HDR brachytherapy modalities were compared based on the percentage of patients reaching the target clinical goal for $D_{90} \text{CTV}_{\text{HR}}$. The best experimental brachytherapy modality was selected for further analysis. If similar results were obtained, the PDR plan with the lower number of pulses was selected.

Determination of the group of high risk patients benefiting the most from the PDR modality:

For binary classification, patients who did not achieve the $D_{90} \text{CTV}_{\text{HR}}$ clinical goal and who had an increase in TCP greater than 3% were considered to benefit from PDR. Preplan variables as well as clinical variables were assessed using a correlation matrix and principal component analysis to shrink the potential variables of interest.

Once the variables were selected, optimal cutpoints based on specificity were determined using the "cutpointr" R package. Then, two arms were created, the preplan arm treated with HDR and its paired experimental arm treated with PDR.

Preplan and experimental arms were compared for $D_{90\%} \text{HR CTV}$ and TCP using a paired t-test.

Sensitivity analysis

To determine how $D_{90\%} \text{HR CTV}$ and TCP are affected by radiobiological parameters, alternative EQD2 estimations were calculated for the high-risk group, using different values for α/β ratio and $T_{1/2}$.

Statistical analysis:

All statistical analyses were performed using Rstudio 2022.07.2.(149) The data were presented as the mean with standard deviation or median with interquartile range (IQR) for continuous variables and as frequencies (percentages) for categorical variables. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant. The feasibility of a randomized clinical trial comparing HDR vs PDR for local-free survival with Cox model in this high-risk population was assessed. Sample size was calculated from the theoretical hazard ratio estimated following the TCP model. Sample size calculation was performed using the "gsDesign" R package, based on methods described in Jennison et al.(181,182)

3.2.4 Results

Patient and tumors characteristics:

From December 2018 to May 2020, 50 consecutive patients treated for LACC with brachytherapy were included in the study. All patients had previously received concomitant radiochemotherapy to the pelvis at a dose of 45 Gy in 25 fractions of 1.8 Gy. Vaginal mold, Utrecht and Venezia applicators were used for brachytherapy for respectively 35, 8 and 7 patients. Half of the patients (25) had a combined intracavitary and interstitial application. The median number of interstitial needles was 8 (Interquartile [IQR] 6-12). Median CTV_{HR} volume and median CTV_{IR} volumes were 28.1 cc (IQR 18.5-42.4) and 73.8 cc (IQR 51.7-98.1).

Dosimetric results:

Dosimetric results showed that the median D₉₀ CTV_{HR} ranged from 41.2 Gy (IQR 35.1-45.7) for the preplan to 45.7 Gy (IQR 44.1-45.7) for the most protracted PDR plan with 70 pulses, with a percentage of achievement of the optimal objective for CTV_{HR} coverage ranging from 40% to 64%. The median D₉₈ CTV_{IR} ranged from 15.7 Gy (IQR 13.6-17.5) for the preplan to 19.7 Gy (IQR 18.1-21.3) for the 70 pulses PDR plan, with a percentage of achievement of the optimal objective for CTV_{IR} coverage ranging from 52% to 88%. The median D2cc to the bladder, rectum, sigmoid and small bowel were also analyzed, with results indicating a decrease in dose to these organs for PDR plans, which was particularly relevant with increasing number of pulses. The collected metrics are summarized in **Figure 3.2.1**.

Selection of the best experimental brachytherapy modality:

PDR plans with 60 and 70 pulses had the highest probability to reach the target clinical goal for D₉₀ CTV_{HR}, with a success rate of 64%. As a result, the 60 pulses PDR plan was selected as the most effective experimental brachytherapy modality, as shown in **Figure 3.2.2**. The mean D₉₀ CTV_{HR} was 40.0 Gy (SD 7.5) for the 4 fractions HDR preplan and 43.6 Gy (SD 5.03) for the 60 pulses PDR plan. This translated to a mean difference of 3.6 Gy [95% CI (2.6-4.7), p-value <0.0001], in favor of the 60 pulses PDR plan. In terms of TCP at 3 years, the mean was 90.8% (SD 7.0) for the 4 fractions HDR preplan and 92.3% (SD 5.0) for the 60 pulses PDR plan. This would correspond to a mean difference of 1.5% [95% CI (0.9-2.0), p-value

<0.0001]. The comparison between the two modalities are summarized in **Table 3.2.1**.

Selection of the group of high-risk patients most likely to benefit from PDR:

An analysis of the correlation between an increase in TCP and several variables investigated, such as CTV_{HR} volume, CTV_{IR} volume, number of needles, preplan D₉₀ CTV_{HR}, preplan D2cc bladder, and preplan D2cc rectum, revealed Pearson correlation coefficients of 0.81, 0.73, 0.40, -0.82, 0.21, and 0.28, respectively. The correlation matrix is available in **Figure 3.2.3**. The principal component analysis confirmed CTV_{HR} volume and preplan D₉₀ CTV_{HR} as the best complementary variables (illustrated in **Figure 3.2.4**). These two variables were chosen to identify patients who are most likely to benefit from PDR rather than HDR. To select patients with at least a 3% benefit in TCP at 3 years, an optimal cutpoint was determined for HR CTV at 67.5cc, with an accuracy, sensitivity, and specificity of 0.92, 0.50, and 1, respectively. Similarly, an optimal cutpoint was determined for D₉₀ CTV_{HR} at 31.1Gy, with an accuracy, sensitivity, and specificity of 0.92, 0.63, and 1, respectively. By combining these two factors, the selection process had an accuracy, sensitivity, and specificity of 0.96, 0.88 and 0.98 respectively.

Best experimental arm versus the control arm:

Eight patients (16%) with CTV_{HR} volume > 67.5cc or D₉₀ CTV_{HR} dose < 31.1 Gy were identified. Of these patients, five (62.5%) underwent interstitial application, with a median of 15 interstitial needles (IQR 14-15). The median CTV_{HR} and CTV_{IR} volumes were 67.6 cc (IQR 44.1-76.8) and 129.0 cc (IQR 95.3-138.8) respectively.

Comparing the preplan and the 60 pulses PDR modality, the mean D₉₀ CTV_{HR} was 27.7 Gy (SD 6.4) and 34.7 Gy (SD 7.0) respectively. This corresponds to a mean absolute difference of 7.0 Gy [95%CI (6.2-7.7), p-value<0.0001]. The mean TCP at 3 years for the preplan and the 60 pulses PDR modality were 77.9% (SD 6.9) and 82.7% (SD 5.5) respectively. This corresponds to a mean difference of 4.8% [95% CI (3.5-6.1), p-value<0.0001]. The comparison between the two groups are summarized in **Table 3.2.1**.

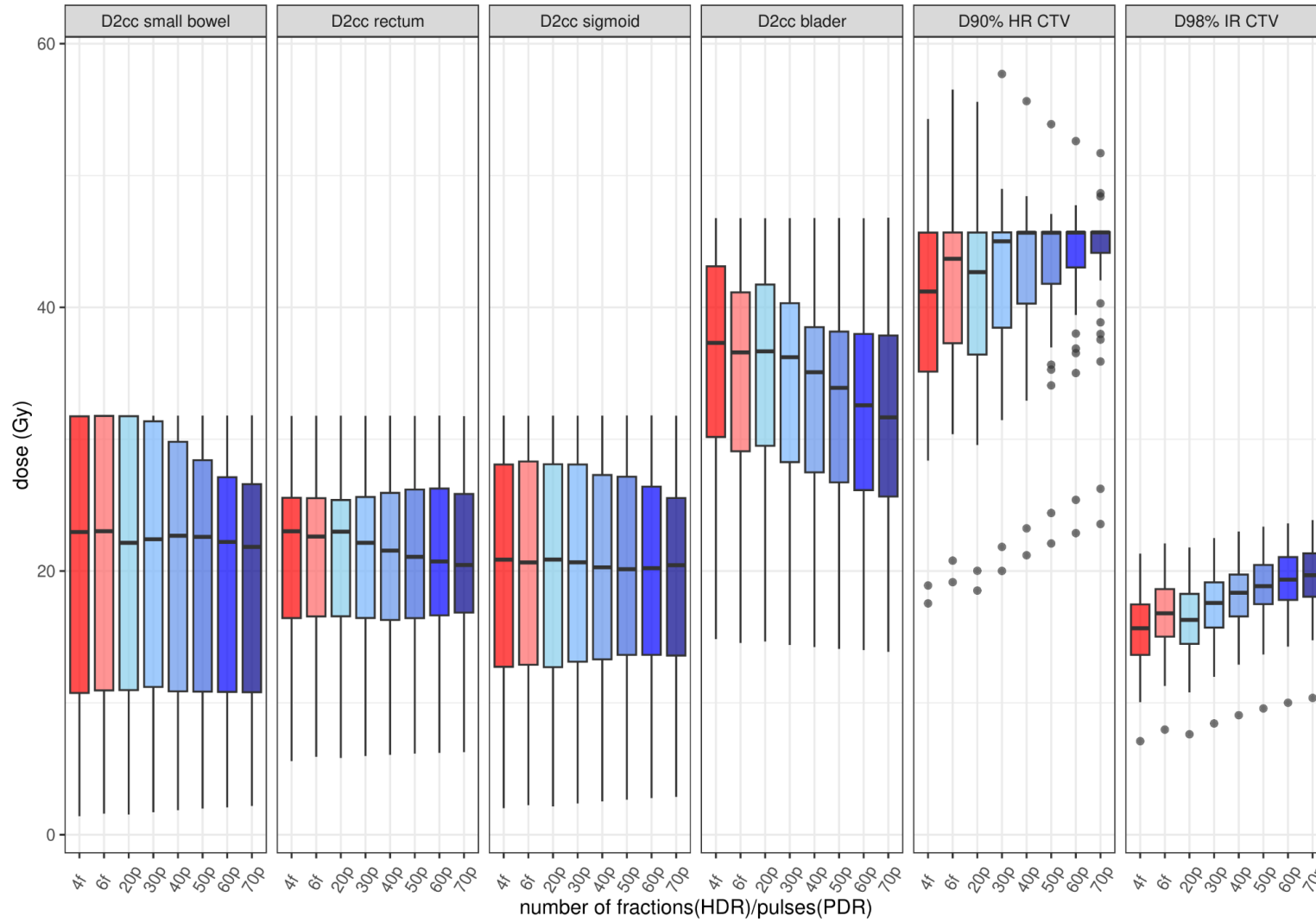


Figure 3.2.1. Boxplot of the metrics. HDR: high-dose-rate, PDR: pulsed-dose-rate, CTV_{HR}: high risk clinical target volume, CTV_{IR}: intermediate risk clinical target volume.

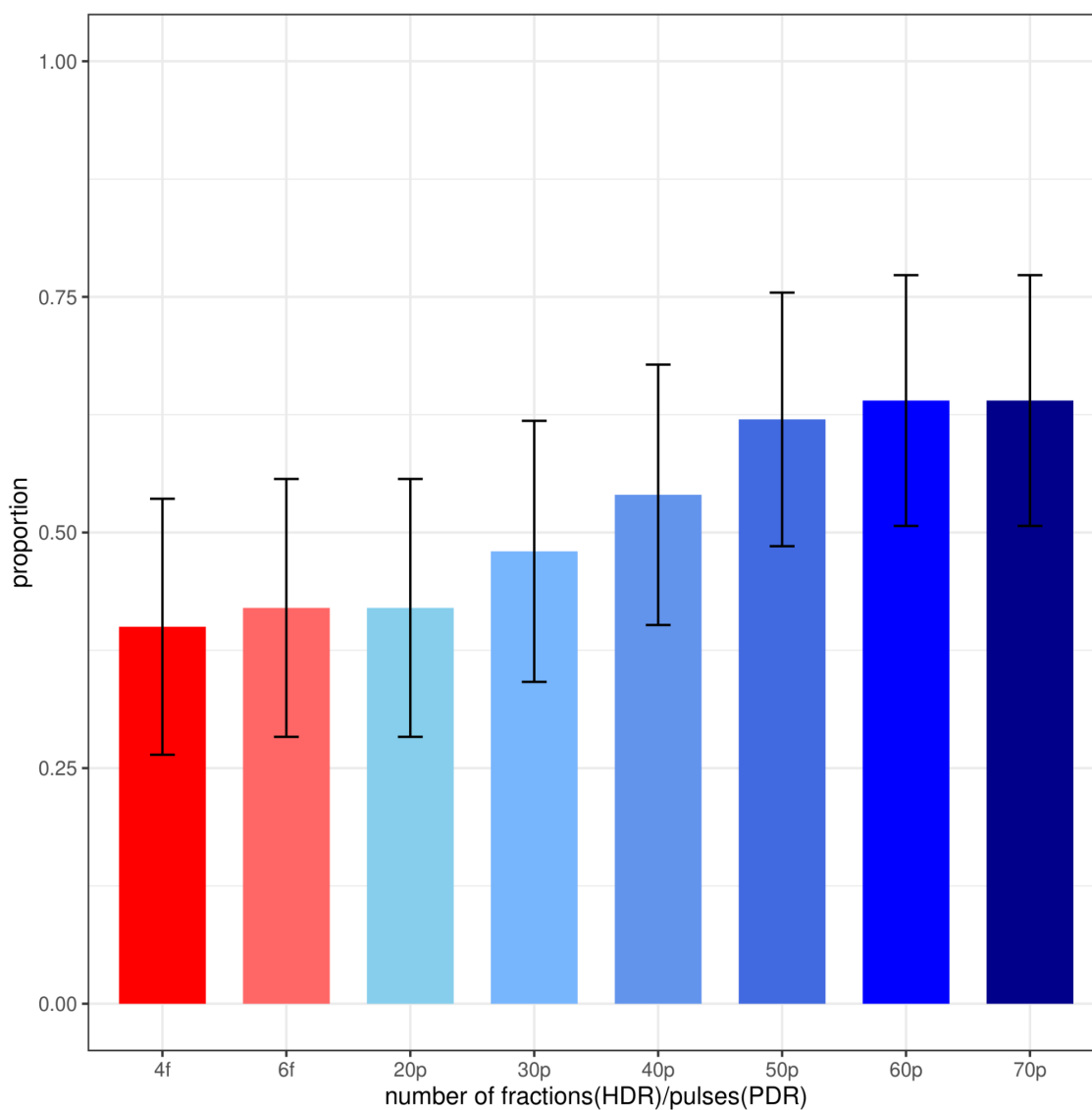


Figure 3.2.2. Histogram of patients reaching the target clinical goal for $D_{90} CTV_{HR}$. HDR: high-dose-rate, PDR: pulsed-dose-rate.

	Overall population			High risk patients		
	HDR (4 fractions) N = 50	PDR (60 pulses) N = 50	p-value (paired t test)	HDR (4 fractions) (N = 8)	PDR (60 pulses) (N = 8)	p-value (paired t test)
D₉₀ CTV_{HR} (Gy)						
median (IQR)	41.2 (35.1-45.7)	45.7 (43.0-45.7)		28.6 (26.0-31.4)	36.7(32.6-38.4)	
mean (SD)	40.0 (7.5)	43.6 (5.0)	<0.0001	27.7 (6.4)	34.7 (7.0)	<0.0001
D₉₈ CTV_{IR} (Gy)						
median (IQR)	15.7 (13.6-17.5)	19.3 (17.8-21.1)		11.8 (10.3-13.4)	16.3 (14.3-18.5)	
mean (SD)	15.4 (3.1)	19.0 (2.8)		11.3 (2.6)	16.0 (3.3)	
TCP (%)						
median (IQR)	93.5 (90.8-95.0)	94.1 (92.6-95.4)		77.8 (75.5-79.7)	83.0 (81.5-83.5)	
mean (SD)	90.8 (6.7)	92.3 (5.1)	<0.0001	77.9 (6.9)	82.7 (5.5)	<0.0001
Bladder D2cc (Gy)						
median (IQR)	37.3 (30.2-43.1)	32.6 (26.1-38.0)		41.1 (38.2-46.7)	39.8 (37.3-46.7)	
mean (SD)	35.5 (9.4)	32.4 (8.8)		40.9 (6.2)	40.4 (6.2)	
Rectum D2cc (Gy)						
median (IQR)	23.0 (16.4-25.6)	20.7 (16.6-26.3)		24.5 (23.0-26.0)	25.6 (23.9-27.4)	
mean (SD)	21.1 (7.0)	20.6 (6.6)		24.3(4.9)	25.5 (4.5)	
Small bowel D2cc (Gy)						
median (IQR)	23.0 (10.8-31.7)	22.2 (10.8-27.1)		10.8 (4.1-31.8)	12.4(5.58-31.7)	
mean (SD)	20.0 (10.8)	19.3 (9.8)		16.6 (14.4)	17.4 (13.8)	
Sigmoid D2cc (Gy)						
median (IQR)	20.9 (12.7-28.1)	20.2 (13.6-26.4)		19.9 (16.2-27.1)	21.7 (18.4-27.7)	
mean (SD)	20.3 (8.7)	19.9 (8.0)		19.7 (9.6)	20.9 (9.25)	

PDR: pulsed dose rate, HDR: high dose rate, TCP: tumor control probability, CTV_{HR}: high risk clinical target volume, CTV_{IR} intermediate risk clinical target volume, cc: cubic centimeter, Gy: Gray, IQR: interquartile range, SD: standard deviation.

Table 3.2.1. Metrics and Tumor Control Probability

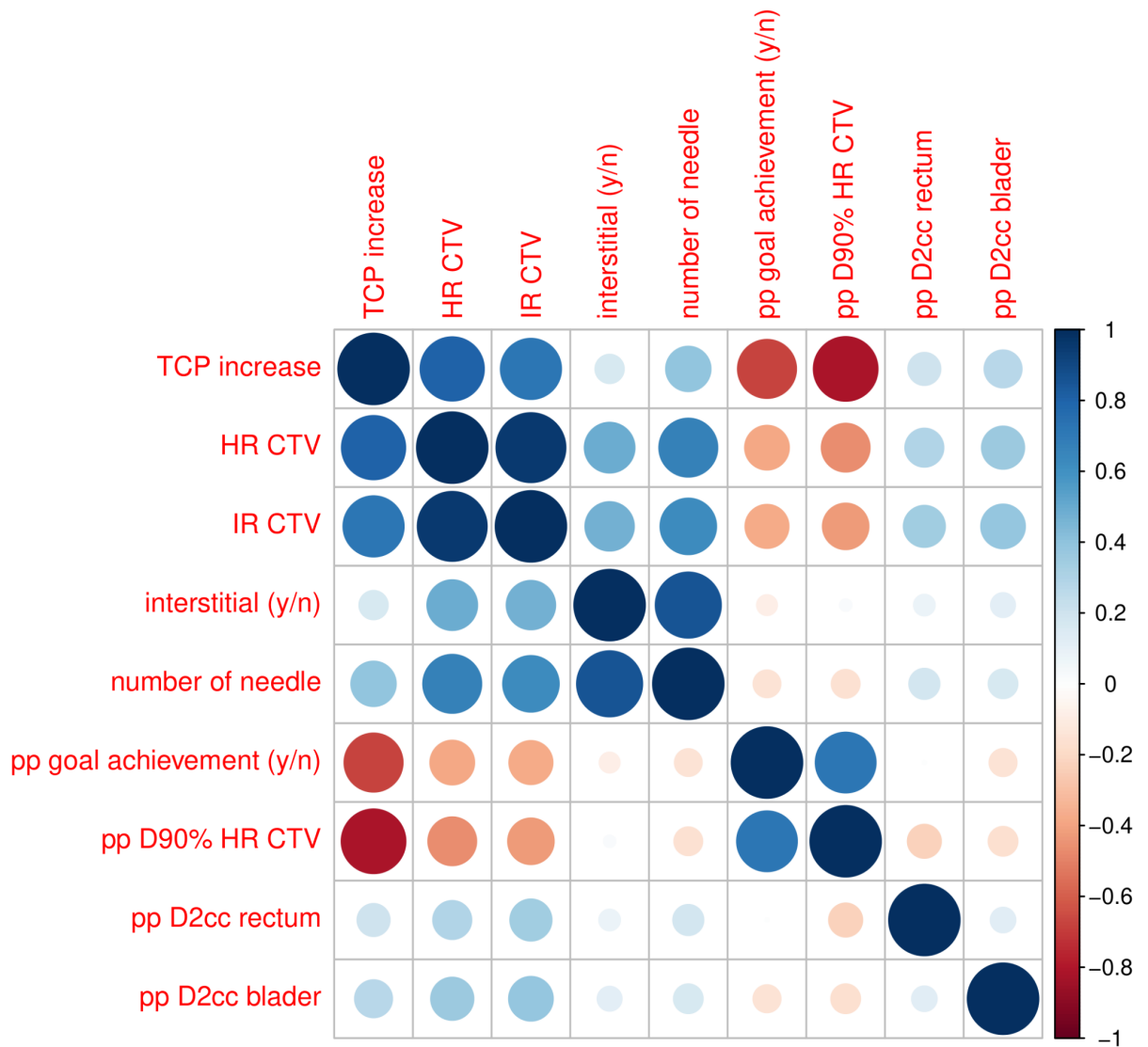


Figure 3.2.3. Correlation Matrix between TCP Increase and several variables. pp: preplan, HDR: high-dose-rate, PDR: pulsed-dose-rate, CTV_{HR} : high risk clinical target volume, CTV_{IR} : intermediate risk clinical target volume, TCP: tumor control probability.

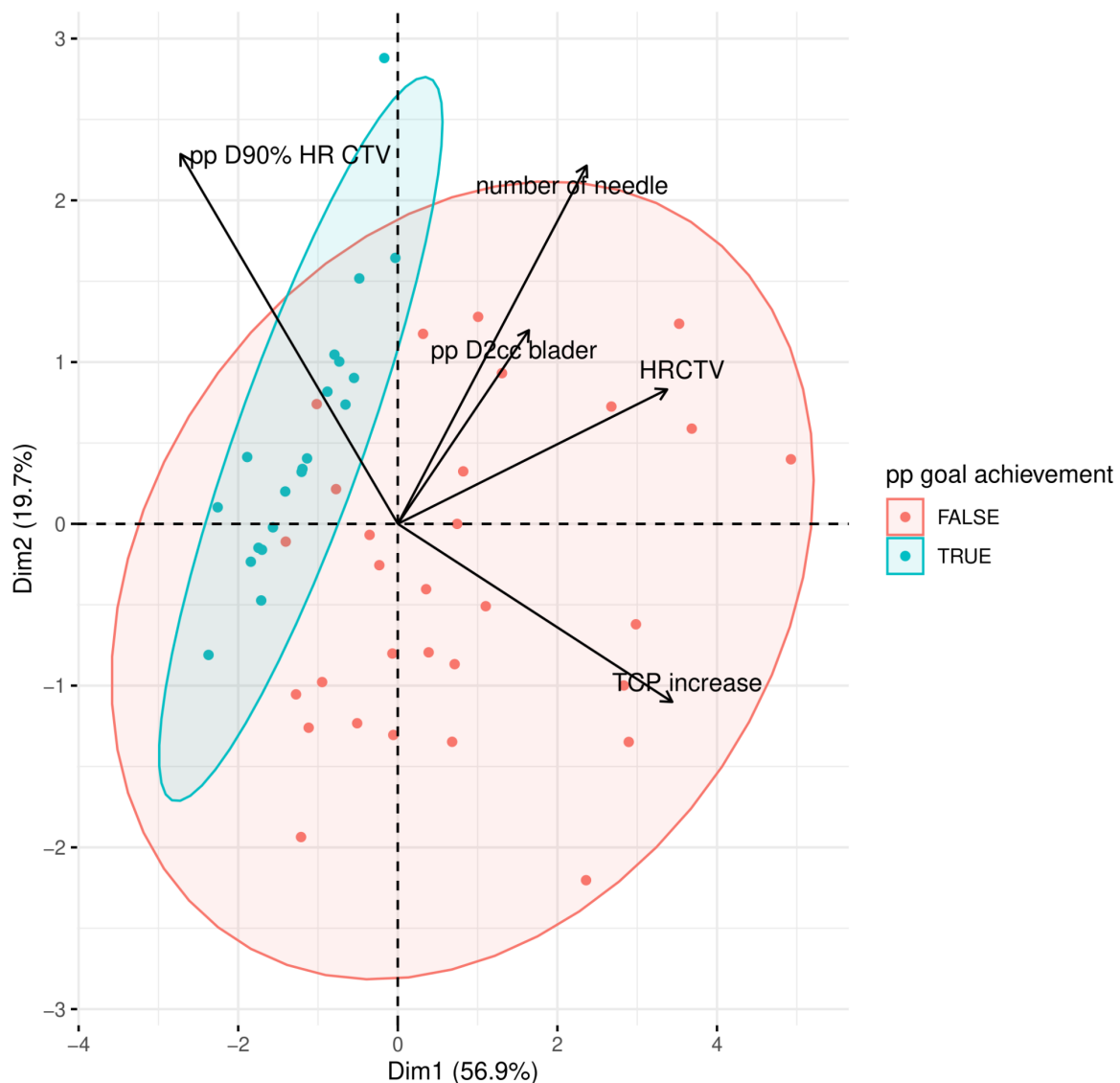


Figure 3.2.4. Principal Component Analysis. pp: preplan, TCP: tumor control probability, CTV_{HR} : high risk clinical target volume.

Sensitivity analysis

For a constant α/β ratio of 10, the mean $D_{90} CTV_{HR}$ for the HDR plan was 27.7 Gy (SD 6.4), while the mean $D_{90} CTV_{HR}$ for the PDR plan was 30.4 Gy (SD 5.6), 34.7 Gy (SD 7.0), and 40.8 Gy (SD 8.9) for $T_{1/2}$ of 0.5h, 1.5h, and 3h, respectively. The mean TCP for the HDR plan was 77.9 % (SD 6.9), while the mean TCP for the PDR plan was 79.8% Gy (SD 6.7), 82.7% (SD 5.5), and 86.1% (SD 4.3), respectively.

For a constant $T_{1/2}$ of 1.5, the mean $D_{90} \text{CTV}_{\text{HR}}$ for the HDR plan was 36.5 Gy (SD 10.0), 29.8 Gy (SD 7.3) and 27.7 Gy (SD 6.4) for α/β ratio of 3, 7, and 10, respectively. The mean $D_{90} \text{CTV}_{\text{HR}}$ for the PDR plan was 36.3 Gy (SD 8.6), 35.1 Gy (SD 7.4), and 34.7 Gy (SD 7.0), respectively. The mean TCP for the HDR plan was 83.8% (SD 4.8), 79.5% (SD 6.3) and 77.9% (SD 6.9), respectively. The mean TCP for the PDR plan was 83.7% (SD 8.6), 82.9% (SD 5.3), and 82.7% (SD 5.5), respectively.

Alternative EQD2 and TCP estimation calculated using other values of α/β ratio and $T_{1/2}$ are illustrated in **Figure 3.2.5**. The impact to the OARs is illustrated in **Figure 3.2.6** and **Figure 3.2.7**.

Feasibility of a randomized clinical trial:

To achieve a power of 80%, with a randomization ratio of 0.5 and a two-sided alpha risk of 5%, a fixed accrual and study duration of 3 and 8 years respectively, the study would require 480 events. This would translate to a sample size of 1230 patients. Assuming a dropout rate of 0.2, a total of 1475 patients would need to be enrolled in the study.

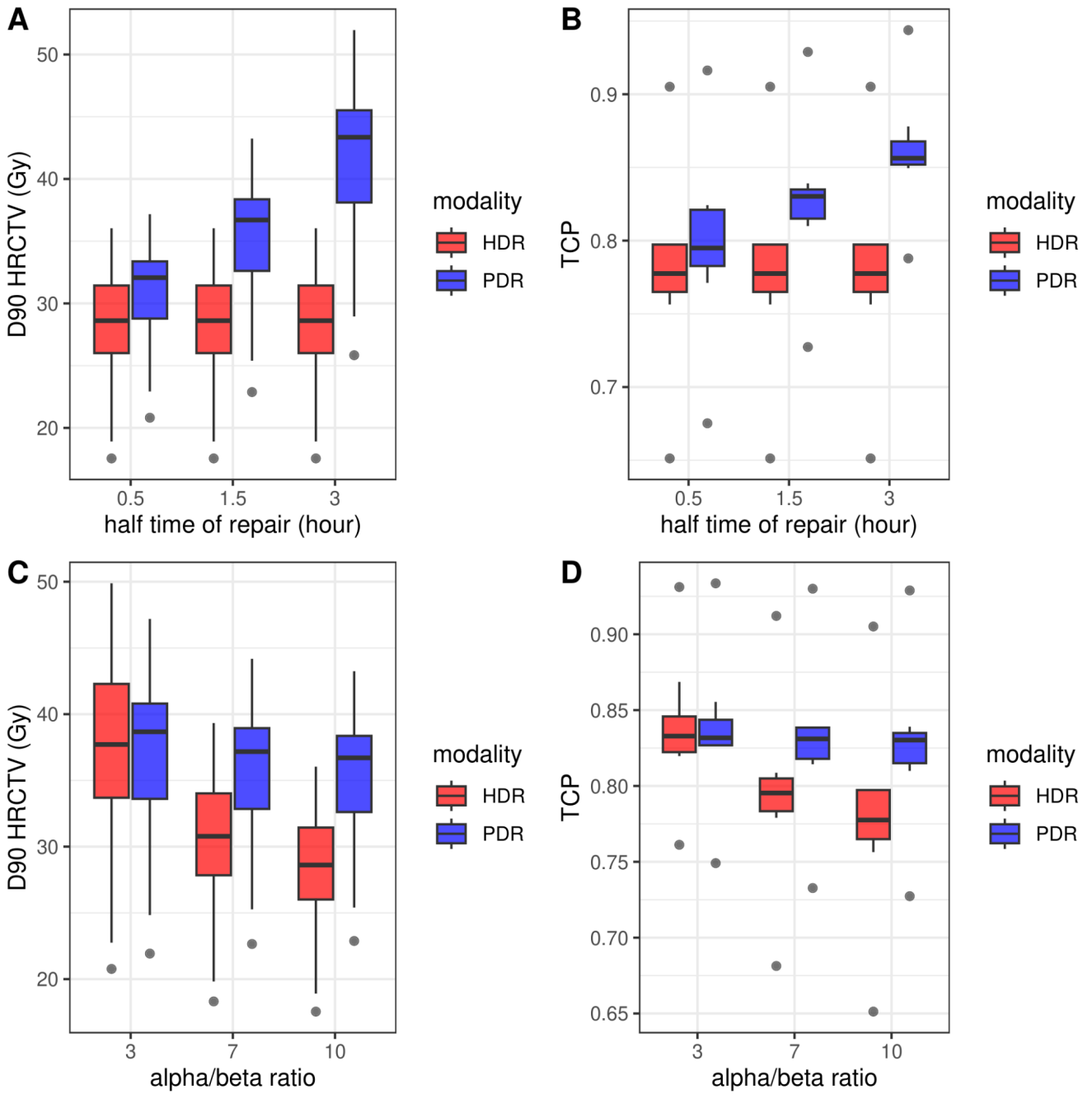


Figure 3.2.5. Alternative D_{90} CTV_{HR} EQD2 and TCP estimation calculated using other values of α/β ratio and $T_{1/2}$. HDR: high-dose-rate, PDR: pulsed-dose-rate

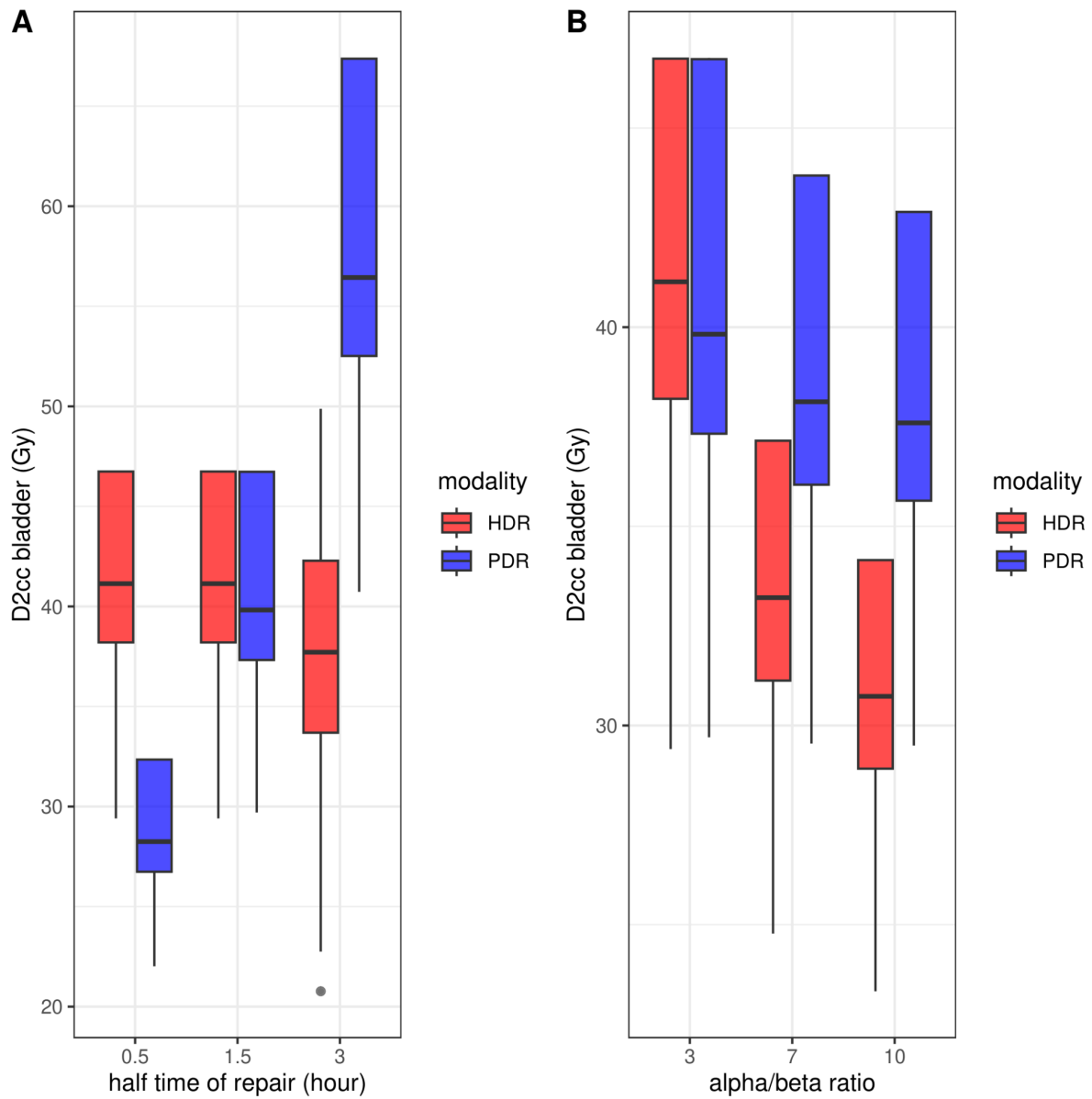


Figure 3.2.6. Alternative D_{2cc} bladder EQD2 calculated using other values of $T_{1/2}$ (A) and α/β ratio (B). HDR: high-dose rate, PDR: pulsed-dose-rate.

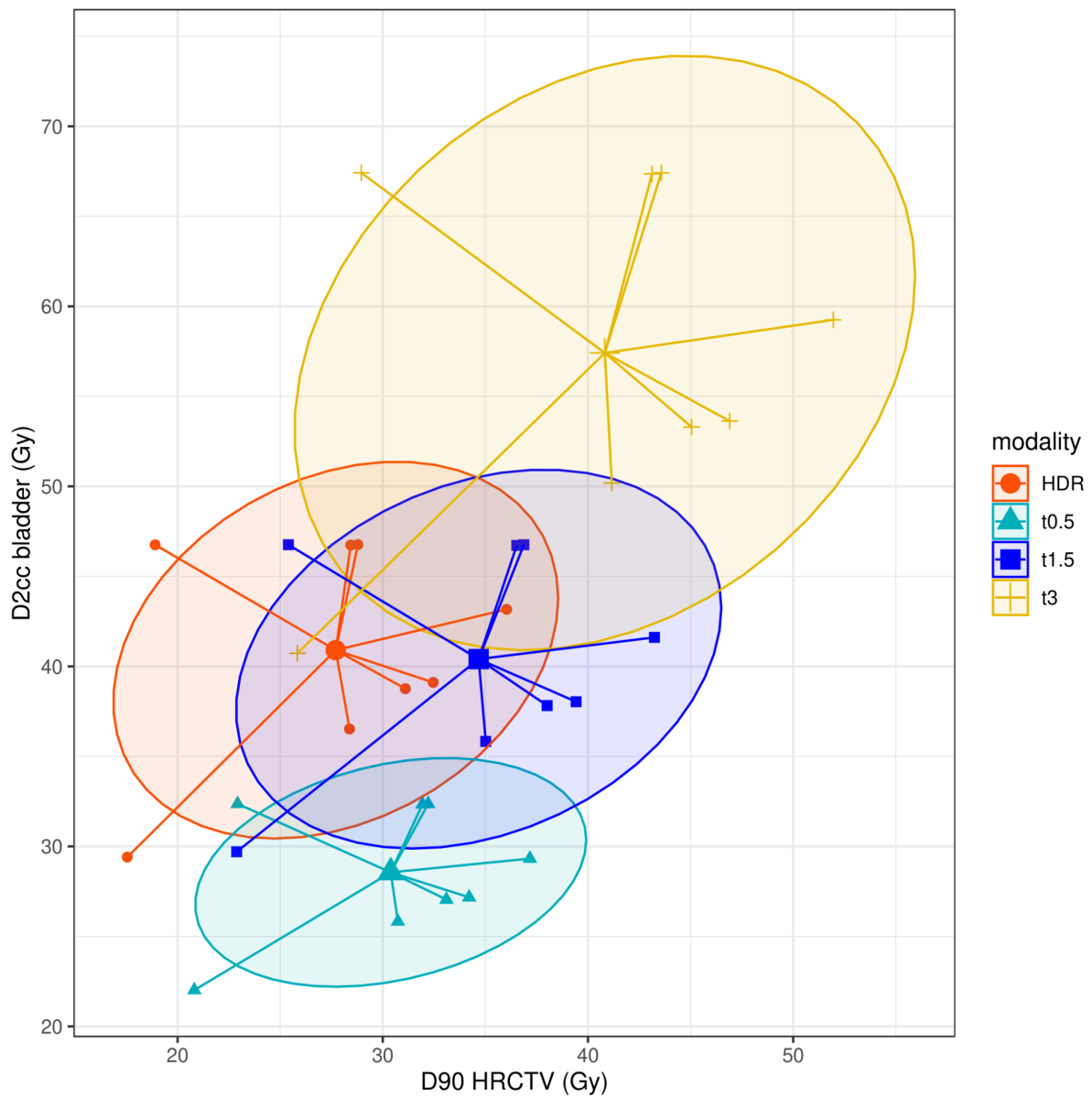


Figure 3.2.7. D_{2cc} bladder EQD2 function of D_{90} CTV_{HR} EQD2. EQD2 calculated using α/β ratio of 3 Gy for the bladder and 10 Gy for D_{90} CTV_{HR} . For PDR, alternative EQD2 were calculated using values of $T_{1/2}$ ranging from 0.5h to 3h. HDR: high-dose rate

3.2.5 Discussion

This study provides novel insight into the theoretical benefits of PDR for patients with locally advanced disease treated with dose escalation through magnetic resonance imaging-based adaptive techniques and interstitial implantation. Our results showed that PDR plans with 60 pulses were the most effective in achieving the target clinical goal for $D_{90} \text{CTV}_{\text{HR}}$ without exceeding OARs dose constraints. The study also identified factors such as CTV_{HR} volume $> 67.5\text{cc}$ or $D_{90} \text{CTV}_{\text{HR}} < 31.1 \text{ Gy}$ on a HDR pre-plan as the best indicators for identifying patients who are likely to experience a greater than 3% increase in TCP with a PDR irradiation. The selection process had an accuracy of 0.96, sensitivity of 0.88, and specificity of 0.98. However, only 8 out of 50 patients (16%) were found to potentially benefit from PDR over HDR, with a mean $D_{90} \text{CTV}_{\text{HR}}$ of 7 Gy higher and a mean TCP at 3 years of 4.8% higher for the PDR plan compared to the HDR preplan.

Our results showed that there was a relevant theoretical benefit of PDR for only a small subset of patients. This can be explained by the use of interstitial implantation and modulation techniques, which have potentially narrowed the gap between PDR and HDR. This is confirmed by the fact that using CTV_{HR} volume alone as a selection criterion provides poor performance in identifying the best patients for PDR treatment.

LDR brachytherapy was the original form of brachytherapy, which was the basis for most radiobiological or clinical studies. From a radiobiological perspective, non-clinical studies comparing the therapeutic ratio of HDR vs LDR found a theoretical advantage in favor of LDR.(86–88) Despite this theoretical superiority, randomized trials and meta-analyses on cervical cancer patients failed to show an increased toxicity rate with HDR brachytherapy.(89–92) A more recent study concluded that HDR intracavitary brachytherapy was superior to LDR in terms of late rectal and bladder complications, while local control rates and survival were similar.(183) One possible explanation for these results is that HDR, contrary to LDR, allowed for the adjustment of dwell times and positions, resulting in an optimized dose distribution that counterbalances its radiobiological disadvantage. As a result, HDR is currently preferred worldwide over other forms of brachytherapy, despite its theoretical radiobiological limitations.

PDR combines the radiobiological advantage of LDR with added benefits of HDR in terms of dose optimization and radiation protection. However, to the best of our knowledge, only one prospective trial comparing HDR to PDR in patients with locally advanced cervical cancer has been published. In this randomized study, the HDR arm received three fractions delivering 7 Gy to "point A" while the PDR arm received 39 pulses delivering 0.7 Gy each. While a large trend in favor of PDR was observed in terms of toxicity, statistical significance was not reached due to the low sample size of the study.(95) No recent clinical trial has explored this issue with modern treatment including dose escalation strategy based on MRI adaptive brachytherapy and interstitial implantation. As a result, despite its theoretical advantages, the use of PDR is decreasing worldwide due to logistical and economic considerations as well as a lack of clinical evidence.

However PDR-brachytherapy is still preferred for treating sensitive areas such as the anal canal, penile glans, vagina, oral mucosa or for reirradiation.(3,97) It is important for the brachytherapy community to continue promoting PDR-brachytherapy, particularly for the treatment of pediatric cancers. Currently, institutions have the option to choose between VLDR, HDR, and PDR for their brachytherapy equipment. The decision takes into account both cost-utility and the center's activity. Therefore, identifying a group of cervical cancer patients who benefit from PDR over HDR could be crucial in the decision to keep the PDR modality.

The primary drawback of this study lies in its reliance on the linear quadratic model, which involves making an estimate of the α/β ratio and the halftime of tissue repair. This estimate may be incorrect. If the halftime of tissue repair is overestimated, the resulting PDR EQD2 values would be lower and may result in an overestimation of the impact on the tumor. However, this would not necessarily result in a significant reduction of the therapeutic window, as the halftime of tissue repair for late reactions in OARs may also be overestimated. Another limitation of the study is the use of an unvalidated TCP model. TCP models predict the probability of tumor control under a particular treatment, but their validity depends on their ability to accurately reflect reality. If they are not externally validated, their predictions may not be trustworthy and could lead to inaccuracies in the analysis of outcomes. Although

the parameters of the model in this study were extracted from a high-quality multi-center study, the inherent biases of a retrospective study remain.(180) Additionally, the prevalence of interstitial needle usage may have changed since the time of data collection, which could have impacted dose distribution and altered the dose-response relationship in our study, where 50% of patients had interstitial components.

Only clinical trials can provide strong evidence, but based on our findings, the sample size required would be too large to be feasible. This is because such trials require that enrolled patients have access to both modalities of brachytherapy, which may not be possible given the current availability of care worldwide. Another solution would be to enhance understanding of radiobiology, specifically regarding the parameters of the linear quadratic model. This progress could be achieved by utilizing the large data collected within EMBRACE studies.

In conclusion, this study highlights the potential of a pre-plan approach to enhance the benefits of PDR. Further research on the linear quadratic model is crucial to fully understand its capabilities and translate these findings into a clinical practice. Such findings would help to sustain the role of PDR in the world of brachytherapy.

Conclusion

This thesis offers a comprehensive analysis of the impact of dose rate in brachytherapy, examining the advantages and disadvantages of two brachytherapy modalities, HDR and PDR, and exploring potential improvements in treatment outcomes for LACC patients through personalized treatment planning.

Within the context of brachytherapy treatments, the dose/rate effect has been the primary focus of radiobiological research, while data on other radiobiological factors influencing brachytherapy's effects are limited. Preclinical studies have demonstrated the theoretical radiobiological advantage of PDR brachytherapy. Biological models based on the linear quadratic model and the incomplete repair model provide estimations of optimal settings for brachytherapy modalities. Moreover, predictive models exist to assess the probability of normal tissue complications and local tumor control. Combining these two approaches should help to determine the most appropriate brachytherapy modality for specific situations.

Despite the promising preclinical data, there is a significant lack of clinical evidence supporting the radiobiological superiority of PDR brachytherapy. This research gap can be attributed to various factors, such as challenges in designing and conducting adequately powered randomized clinical trials, logistical and economic constraints related to PDR, and the rapid evolution of treatment techniques. As a result, translating preclinical findings into clinical practice remains uncertain, highlighting the need for well-designed clinical studies to validate PDR brachytherapy's potential benefits and determine its optimal use in patient care.

Our meta-analysis of anal canal cancer patients, though not conclusively establishing the superiority of PDR brachytherapy over HDR, provides valuable insights into PDR's potential clinical advantages. We found that PDR allowed for significantly higher radiation doses than HDR, facilitating dose escalation and achieving similar local control levels for both advanced and early-stage tumors without increasing late side effects. These findings support PDR's potential clinical benefits and align with radiobiological models predicting an improved therapeutic window with PDR.

The thesis also explores the potential of PDR brachytherapy in enhancing local control in a subset of LACC patients without increasing the risk of side effects. On the other hand, this work emphasized that interstitial needle usage and modulation techniques may have narrowed the theoretical gap between PDR and HDR brachytherapy. We identified factors such as CTVHR volume > 67.5cc or D90 CTVHR < 31.1 Gy on an HDR pre-plan as the best indicators for pinpointing patients who might benefit from PDR brachytherapy.

However, the thesis also underscores the limitations of the linear quadratic model, which could result in inaccuracies in outcome analysis. Moreover, conducting a randomized clinical trial to provide robust evidence on PDR's benefits remains challenging due to the required large sample size and the global availability of PDR modality.

To fully comprehend the potential advantages of PDR and incorporate these findings into clinical practice, further research on the linear quadratic model and radiobiology is essential. Such findings would help maintain the role of PDR in the brachytherapy landscape and potentially improve treatment outcomes for LACC patients.

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Appendix

Appendix 1. R script chunk developed for extracting brachytherapy dosimetric data from ".dvh" files.

```
### dataset

## list.files() : vector of the dosimetric ".dvh" files
fid <- list.files("data/dosiPDR/dosi", pattern="*.txt",
full.names=TRUE)

##patient ID extraction
fn<-regmatches(fid, regexpr("[0-9].*[P]", fid))

## creation of the metrics using "DVHmetrics" package
library(DVHmetrics)
metm<-function(y) {
  d <-readDVH(y,type = "Masterplan")
  names(d)<-fn
  D90CTVhr<-getMetric(d, metric = "D90%",structure="CTVhr")
  D98CTVir<-getMetric(d,metric = "D98%",structure="CTVir")
  D2cc<-getMetric(d,metric = "D2cc",structure=c("Rectum",
"Sigmoide", "Vessie", "Grele"))
  Vctvhr<-getMetric(d,metric= "V0.2Gy_CC", structure="CTVhr")
  Vctvir<-getMetric(d,metric= "V0.3Gy_CC", structure="CTVir")
  md<-rbind(D90CTVhr,D98CTVir,D2cc,Vctvhr,Vctvir)
  return(md)
}
dpw<-metm(y = fid)
tail(dpw)

## extraction of brachytherapy modalities (regular expression
# inside file name)
dpw$IPP<-regmatches(dpw$patID, regexpr("[0-9]*[0-9]",
dpw$patID))
npulses<-regmatches(dpw$patID, regexpr("[0-9]*[P]",
dpw$patID))
dpw$npulses<-regmatches(npulses,regexpr("[0-9]*[0-9]",
npulses))
dpw$BTmodality<-grepl("hdr", dpw$patID, ignore.case = TRUE)
dpw$BTmodality[dpw$BTmodality==TRUE]<-"HDR"
```

```

dpw$BTmodality[dpw$BTmodality==FALSE]<-"PDR"

# attribution of alpha/beta value
library(stringr)
dpw$ab<-rep("NA",length(dpw[,1]))
isctv<-str_detect(dpw$structure,regex("CTV",dotall=T))
dpw[isctv,"ab"]<-rep(10, length(isctv[isctv=="TRUE"]))
dpw[!isctv,"ab"]<-rep(3, length(isctv[isctv=="FALSE"]))

# number of pulses
dpw$npulses<-as.numeric(dpw$npulses)
dpw$ab<-as.numeric(dpw$ab)
#dose/pulse > total dose
dpw$x<-dpw$observed*dpw$npulses

# brachytherapy parameters and metrics (physical dose) stored
in dpw

```

Appendix 2. R script chunk developed for converting brachytherapy physical dose to EQD2

```
### EQD2
## PDR
# x = dose, ab = alpha/beta ratio, npulses = number of pulses,
# tdemi = T1/2 (h), itpulse = pulse irradiation time (h),
# rtpulse = pulse repetition time

POWER<-function(num, pow) {
  res<-num^pow
  return(res)
}
eqd2PDR<-function(x, npulses, ab, tdemi, itpulse, rtpulse) {
  dpulse<-x/npulses
  m<-log(2, base = exp(1))/tdemi
  form1<-1-exp(-m*itpulse)
  form2<-exp(-m*(rtpulse-itpulse))
  form3<-(npulses*form2-form2-npulses*form2*form2*exp(-m*itpulse
)+ POWER(form2, (npulses+1))*exp(-m*npulses*itpulse))/
  (POWER((1-form2*exp(-m*itpulse)), 2))
  form4<-2/npulses/m/itpulse*(1-(npulses*form1-form3*form1*form1
)/(npulses*m*itpulse))
  bed<-npulses*dpulse*(1+form4*npulses*dpulse/ab)
  eqd2<-bed/(1+2/ab)
  return(eqd2)
}

# attribution of PDR modality parameters
dpwp<-dpw[dpw$BTmodality=="PDR", ]
dpwp$tdemi<-rep(1.5, length(dpwp$IPP))
dpwp$itpulse<-rep(0.3, length(dpwp$IPP))
dpwp$rtpulse<-rep(1, length(dpwp$IPP))

library(dplyr)
dwp<-mutate(dpwp, value=eqd2PDR(x, npulses, ab, tdemi, itpulse, rtpu
lse))
colnames(dwp)[c(9, 13)]<-c("pdose", "edose")
dwp$variable<-paste(dwp$metric, dwp$structure)
# PDR EQD2 stored in dwp

## HDR
eqd2HDR<-function(x, ab, npulses) {
  dfraction<-x/npulses
```

```

bedfraction<-dfraction*(1+dfraction/ab)
eqfraction<-bedfraction/(1+2/ab)
eqd2<-eqfraction*npulses
return(eqd2) }
dpwh<-dpw[dpw$BTmodality=="HDR",]
dwh<-mutate(dpwh,value=eqd2HDR(x,ab,npulses))
colnames(dwh)[c(9,10)]<-c("pdose","edose")
dwh$variable<-paste(dwh$metric,dwh$structure)
# HDR EQD2 stored in dwh

# bind dwp (PDR) & dwh (HDR)
dw<-rbind(dwh,dwp[c("observed","metric","structure","patID","I
PP","npulses","BTmodality","ab","pdose","edose","variable")])

```

Appendix 3. R script chunk developed to set TCP model from Tanderup et al., 2016.

```
###TCP data
##Tanderup 2016, cox model, 3yLCFS  $\lambda(t|X) = \lambda_0(t)e^{\beta}$ 
# 3y LC= lambda0(3y) x exp(Beta hrctv*X1 + Beta ctvhrd90*X2 +
Beta OTT*X3)
B_hrctv <-log(1.021)
B_ctvhrd90 <- log(0.965)
B_OTT<-log(1.027)

# lambda0(3y)estimated using 3 points
lambda_3y<-1-0.8656015
lambda0_3y_1<-lambda_3y/exp(B_hrctv*62.81407 + B_ctvhrd90*85 +
B_OTT*49 )
lambda_3y<-1-0.8900376
lambda0_3y_2<-lambda_3y/exp(B_hrctv*52.76382 + B_ctvhrd90*85 +
B_OTT*49)
lambda_3y<-1-0.9285714
lambda0_3y_3<-lambda_3y/exp(B_hrctv*31.15578 + B_ctvhrd90*85 +
B_OTT*49)
lambda0_3y=mean(c(lambda0_3y_1,lambda0_3y_2,lambda0_3y_3))

# formula TCP (3yLC)
TCP<-function(lambda0_3y,B_hrctv,B_ctvhrd90,B_OTT,edose.D90_CT
Vhr,hrctv) {
  lambda_3y<-lambda0_3y*exp(B_hrctv*hrctv +
B_ctvhrd90*(44.3+edose.D90_CTVhr) +
  B_OTT*49)
  return(1-lambda_3y)
}
TCP_60P<-TCP(lambda0_3y=lambda0_3y,B_hrctv=B_hrctv,B_ctvhrd90=
B_ctvhrd90,B_OTT=B_OTT,
  edose.D90_CTVhr=dpca$edose.D90_CTVhr,
  hrctv=dpca$hrctv)
TCP_4F<-TCP(lambda0_3y=lambda0_3y,B_hrctv=B_hrctv,B_ctvhrd90=B
_ctvhrd90,B_OTT=B_OTT,
  edose.D90_CTVhr=dpca$deHRctv4,
  hrctv=dpca$hrctv)
dpca$increase_TCP<-(TCP_60P-TCP_4F)*100
```

Appendix 4. R script chunk developed for sample size estimation from survival time published by Tanderup et al., 2016.

```
### sample size estimation for clinical trial
## probability of survival at a time t
t<-3

## median survival time estimate for LCFS CONTROL
p=mean(TCP_cont)
mc_LCFS<-t*(log(0.5)/log(p))
mc_LCFS

## median survival time estimate for LCFS EXPERIMENTAL
p=mean(TCP_exp)
me_LCFS<-t*(log(0.5)/log(p))
me_LCFS

## hazard ratio rate from LCFS
HR_control_at_t<- -1*log(x=mean(TCP_cont),base=exp(1))/t
HR_exp_at_t<- -1*log(x=mean(TCP_exp),base=exp(1))/t
HR_ratio<-HR_exp_at_t/HR_control_at_t

## sample size
library(gsDesign)
ns<-nSurvival(lambda1= HR_control_at_t,
              lambda2= HR_exp_at_t,
              Ts= 3+5,#max study duration
              Tr= 3,#accrual duration
              ratio= 0.5,#exp/control
              alpha= 0.05,
              sided= 2,
              beta= 0.2
              )
number_pat<-ns$n
drop_out_rate<-0.2
corrected_n<-number_pat+number_pat*drop_out_rate
```

Long résumé en Français

Introduction

Le cancer du col de l'utérus est un problème de santé publique important, en particulier dans les pays en développement où il est l'une des principales causes de décès liés au cancer chez les femmes. Le traitement standard pour le cancer du col de l'utérus localement avancé (CCLA) comprend une combinaison de chimiothérapie et de radiothérapie externe (RTE), suivie d'une curiethérapie, une forme de radiothérapie interne qui implique le placement de sources radioactives scellées à l'intérieur ou à proximité immédiate de la tumeur. La curiethérapie présente plusieurs avantages par rapport à la RTE, notamment une distribution de dose plus conforme, une durée de traitement plus courte et un ratio thérapeutique plus élevé. Elle est également associée à moins d'effets secondaires et de complications par rapport à la RTE, et est considérée comme un standard de soins dans de nombreuses situations. Cependant, il existe plusieurs technologies concurrentes en curiethérapie, telles que la curiethérapie à haut débit de dose (CT-HDD), la curiethérapie à débit de dose pulsé (CT-PDR), la curiethérapie à bas débit de dose (CT-BDD) et la curiethérapie à très bas débit de dose (CT-VLDR), chacune ayant ses propres caractéristiques radiobiologiques et logistiques. Bien que la CT-HDD soit de loin la modalité la plus utilisée, la CT-PDR est encore préférée pour le traitement de zones sensibles telles que le canal anal, le gland, le vagin, la muqueuse buccale, la réirradiation et en particulier pour le traitement des cancers pédiatriques. Cependant, les considérations logistiques et économiques de la CT-PDR limitent son utilisation dans de nombreux centres, et il existe un risque de voir une diminution du nombre d'utilisateurs de la CT-LDR et PDR, ce qui entraînerait le désintérêt de l'industrie vis-à-vis de ces modalités de traitement. Malgré les avantages potentiels de la CT-PDR, sa supériorité par rapport à la CT-HDD n'a jamais été correctement évaluée dans un essai clinique randomisé suffisamment puissant. Même les données rétrospectives comparant les deux modalités sont limitées. L'objectif de cette thèse est d'évaluer le potentiel de la CT-PDR pour le CCLA par le biais des traitements les plus modernes. Pour atteindre cet objectif, trois étapes ont été entreprises.

Premièrement, une revue approfondie des connaissances dans le domaine de la radiobiologie a été réalisée. Deuxièmement, pour obtenir des preuves que la CT-PDR pourrait offrir de meilleurs résultats et vérifier si les connaissances radiologiques sont corroborées par les observations cliniques, une méta-analyse comparant les résultats de la CT-PDR par rapport à la CT-HDD chez les patients atteints de cancer du canal anal a été réalisée. Le canal anal a été sélectionné car nous avons estimé que c'était la localisation présentant la plus forte probabilité d'obtenir des résultats significatifs. Troisièmement, en se basant sur le modèle linéaire quadratique, mais aussi sur un modèle de probabilité de contrôle tumoral (TCP) ainsi que des données dosimétriques de curiethérapie, nous avons défini un sous groupe de patients pouvant bénéficier de la CT-PDR par rapport à la CT-HDD et évalué l'impact clinique théorique.

I. Etat de l'art de la radiobiologie dans le domaine de la curiethérapie

Plusieurs facteurs influencent la réponse des tissus à la curiethérapie, tels que la radiosensibilité des organes à risque et de la tumeur, le débit de dose pour la CT-LDR, la caractéristique des pulses pour la CT-PDR et le fractionnement pour la CT-HDD. En plus du concept des "4R" (réparation de l'ADN, réoxygénation, redistribution du cycle cellulaire et repopulation) de la radiobiologie, d'autres mécanismes biologiques jouent également un rôle dans la réponse des tissus, y compris les interactions dans le microenvironnement cellulaire et les effets potentiels de la réponse immunitaire. L'effet dose/débit a été le paramètre radiobiologique le plus largement étudié dans le contexte des traitements par curiethérapie, avec des données limitées disponibles soutenant l'influence d'autres facteurs radiobiologiques sous-jacents. Des études précliniques ont confirmé la supériorité radiobiologique théorique de la CT-PDR. Des modèles biologiques basés sur le modèle linéaire quadratique et le modèle de réparation incomplète permettent d'estimer les paramètres optimaux pour les modalités de curiethérapie, tandis que des modèles prédictifs existent pour évaluer la probabilité de complications des tissus normaux et de contrôle local de la tumeur. La combinaison de ces deux approches peut être utile pour déterminer la modalité de curiethérapie la plus appropriée pour des situations spécifiques. Néanmoins, il est essentiel de mettre en balance les modèles

radiobiologiques avec le peu de données cliniques à notre disposition, les incertitudes dans la détermination de leurs paramètres ainsi que l'évolution des techniques. Il est primordial d'obtenir davantage de données pour évaluer l'applicabilité de ces résultats dans la pratique clinique.

II. Recherche de preuves de l'intérêt de la curiethérapie PDR

Dans le contexte de l'investigation des bénéfices potentiels de la CT-PDR et de l'obtention de preuves cliniques de sa supériorité, nous avons choisi de nous concentrer sur le cancer du canal anal pour plusieurs raisons. Tout d'abord, cette localisation fournit l'une des plus grandes quantités de données cliniques comparant la CT-PDR et la CT-HDD. Deuxièmement, les implants de curiethérapie utilisés dans le traitement du canal anal sont placés à l'intérieur de l'organe à risque, ce qui en fait un modèle plus pertinent pour évaluer les effets de la CT-PDR sur l'épargne radiobiologique. Troisièmement, le taux de survie sans colostomie est un critère d'évaluation fiable même dans les études rétrospectives, ce qui permet une évaluation plus précise de l'impact thérapeutique. Enfin, contrairement à la curiethérapie du CCLA, la technologie et les méthodes utilisées dans la CT-PDR et HDD du canal anal n'ont pas beaucoup évolué ces dernières années, ce qui garantit que toute différence observée est probablement due aux différences de débits de dose administrés. Ensemble, ces facteurs rendent plus probable l'obtention de résultats statistiquement significatifs par rapport à d'autres localisations. Cette étude a été réalisée en collaboration avec le groupe de travail "PDR" du GEC ESTRO, qui vise à rassembler des données récentes pouvant contribuer à redéfinir le rôle de la CT-PDR dans le monde de la curiethérapie moderne. Dans cette partie, une méta-analyse est présentée comparant les résultats cliniques et les toxicités entre la CT-HDD et la CT-PDR pour le cancer du canal anal. Neuf études rétrospectives avec un total de 481 patients traités ont été incluses, dont 219 patients traités par CT-HDD et 262 avec la CT-PDR. Des différences significatives ont été observées entre les deux groupes pour les caractéristiques de base et le traitement. La proportion cumulée des stades T3-T4 était plus faible dans le groupe HDD, 0,15 (intervalle de confiance à 95 % [IC] de 0,07 à 0,29) contre 0,27 (IC à 95 % de 0,09 à 0,57) dans le groupe PDR, $p < 0,001$. Des doses de curiethérapie plus faibles (EQD2) ont été

administrées aux patients du groupe HDD, 11,9 Gy (IC à 95 % de 8,2 à 15,5) contre 19,5 Gy (IC à 95 % de 15,0 à 24,0) dans le groupe PDR, $p < 0,001$. Aucune différence significative n'a été observée pour les résultats cliniques ou les toxicités. La survie globale à 5 ans pour le HDD et le PDR était respectivement de 0,82 (IC à 95 % de 0,70 à 0,94) et de 0,82 (IC à 95 % de 0,73 à 0,91), $p > 0,99$. Le contrôle local à 5 ans était de 0,86 (IC à 95 % de 0,81 à 0,91) et de 0,83 (IC à 95 % de 0,77 à 0,89), $p = 0,62$. La proportion cumulée de colostomie liée à la toxicité était de 0,04 (IC à 95 % de 0,02 à 0,09) et de 0,03 (IC à 95 % de 0,02 à 0,07), $p = 0,85$. En conclusion, les deux modalités ont montré un bon profil de tolérance et sont des stratégies conservatrices d'organe efficaces pour les patients atteints de cancer du canal anal. En parallèle avec les développements en cours pour mieux déterminer le fractionnement et la dose optimale pour les traitements par CT-HDD, en particulier dans les cas de tumeurs volumineuses, la CT-PDR joue encore un rôle crucial dans la stratégie d'escalade de dose pour les cas avancés. Bien que la supériorité de la CT-PDR par rapport à la CT-HDD reste à confirmer, notre étude chez les patients atteints de cancer du canal anal offre des perspectives importantes sur les bénéfices cliniques potentiels. Nous avons notamment constaté que la CT-PDR permettait d'administrer des doses de radiation significativement plus élevées que la CT-HDD. De plus, notre étude a montré que l'utilisation de la CT-PDR pour l'escalade de dose au-delà des limites habituelles de la CT-HDD pouvait conduire à des niveaux similaires de contrôle local pour les patients atteints de tumeurs très localement avancées par rapport à ceux atteints de tumeurs à un stade précoce. Cela suggère que la CT-PDR peut être une option précieuse pour les patients atteints de maladies avancées qui ne seraient pas candidats à la CT-HDD. Il est également important de noter que l'utilisation de la CT-PDR avec des doses significativement plus élevées que la CT-HDD n'a pas entraîné une incidence plus élevée d'effets secondaires tardifs dans les analyses rapportées.

III. Exploration du bénéfice théorique du PDR dans le CCLA

Dans une première étude, une comparaison des résultats dosimétriques entre la CT-PDR et la CT-HDD a été réalisée à l'aide du modèle linéaire quadratique. Les données dosimétriques tridimensionnelles de 10 patients consécutifs atteints de

cancer du col de l'utérus traités par CT-PDR adaptative guidée par imagerie après RTE ont été examinées. Un nouveau plan HDD a été généré pour chaque patient en utilisant la même méthode que pour le plan PDR tout en ajustant sur la D90 du CTV haut risque. Les résultats ont montré que le CTV à risque intermédiaire (D98) a reçu une dose légèrement plus élevée dans le plan PDR par rapport au plan HDD. De plus, les doses aux organes à risque étaient plus élevées dans les plans HDD pour la vessie, le rectum, le sigmoïde et l'intestin grêle. Lorsque la contribution des organes à risque pour la D2cc était inférieure à 20 GyEQD2, les deux modalités de curiethérapie étaient équivalentes, mais lorsque cette contribution était supérieure à 20 GyEQD2, la CT-PDR présentait un avantage radiobiologique par rapport à la CT-HDD. En conclusion, nos données suggèrent que l'optimisation radiobiologique peut jouer un rôle substantiel dans le processus d'optimisation des traitements par curiethérapie, en particulier dans les cas de tumeurs très avancées. Cela peut se traduire par l'identification de patients qui pourraient bénéficier de la CT-PDR plutôt que de la CT-HDD ou par la possibilité d'effectuer une escalade de dose en ajustant la dose par pulse.

Une seconde étude visait à identifier les facteurs pouvant prédire quels patients atteints de CCLA sont les plus susceptibles de bénéficier de la CT-PDR, et à estimer l'effet différentiel attendu entre les deux modalités de traitement. Cinquante patients consécutifs atteints de CCLA traités par curiethérapie après une RTE ont été inclus dans l'étude. Pour chaque patient, plusieurs plans PDR avec 20 à 70 pulses ont été comparés à un pré-plan HDD en quatre fractions. Un sous-ensemble de patients qui bénéficiait particulièrement de la modalité PDR a été identifié en utilisant des données dosimétriques du pré-plan et des variables cliniques. L'effet clinique attendu a été quantifié à l'aide d'un modèle TCP. Les plans PDR avec 60 pulses se sont avérés les plus efficaces pour atteindre l'objectif clinique pour D90CTVHR. Le volume du CTVHR > 67,5 cc et/ou la D90CTVHR sur le pré-plan HDD inférieure à 31,1 Gy ont été identifiés comme le meilleur indicateur pour sélectionner les patients susceptibles de bénéficier d'une augmentation du TCP de plus de 3 % avec le plan PDR. Le processus de sélection avait une précision de 0,96, une sensibilité de 0,88 et une spécificité de 0,98. Sur les 50 patients inclus dans l'étude, huit (16 %) ont été identifiés comme bénéficiant de la CT-PDR par rapport à la CT-HDD, avec une valeur moyenne de D90CTVHR supérieure de 7 Gy [IC à 95 % (6,2-7,7), valeur $p < 0,0001$]

et une valeur moyenne du TCP à 3 ans supérieure de 4,8 % [IC à 95 % (3,5-6,1), valeur $p < 0,0001$] pour le plan PDR par rapport au pré-plan HDD. Le bénéfice potentiel de la PDR a été fortement influencé par le choix du rapport alpha/bêta et de la période de réparation.

En conclusion, les résultats suggèrent qu'un nombre limité de patients atteints de CCLA bénéficient de la CT-PDR par rapport à la CT-HDD. Le volume de CTVHR et les doses de pré-plan pour le D90CTVHR devraient être considérés comme des facteurs prometteurs dans la sélection de ces patients.

Conclusion

Cette thèse offre une analyse exhaustive de l'impact du débit de dose en curiethérapie sur le traitement du CCLA. Elle examine les avantages et les inconvénients de deux modalités de curiethérapie, HDD et PDR, et explore le potentiel d'une planification personnalisée.

Dans le contexte des traitements par curiethérapie, l'effet dose/débit a été l'objet principal de la recherche radiobiologique, tandis que les données sur d'autres facteurs radiobiologiques influençant les effets de la curiethérapie sont limitées. Les études précliniques ont démontré l'avantage radiobiologique théorique de la CT-PDR.

Malgré les données précliniques prometteuses, il existe un manque significatif de preuves cliniques étayant la supériorité radiobiologique de la CT-PDR. Cela peut être attribué à divers facteurs, tels que les défis liés à la conception et à la réalisation d'essais cliniques randomisés suffisamment puissants, les contraintes logistiques et économiques liées à la CT-PDR, ainsi que l'évolution rapide des techniques de traitement. Par conséquent, la traduction des résultats précliniques en pratique clinique reste incertaine, soulignant la nécessité d'études bien conçues pour valider les avantages potentiels de la CT-PDR et déterminer son utilisation optimale dans les soins apportés aux patients.

Notre méta-analyse des patients atteints de cancer du canal anal, bien qu'elle n'établisse pas de manière concluante la supériorité de la CT-PDR par rapport à la

CT- HDD, offre des perspectives intéressantes sur ses avantages cliniques potentiels. Nous avons constaté que la CT-PDR permettait de délivrer des doses de rayonnement significativement plus élevées que la HDD, facilitant l'escalade de dose et atteignant des niveaux similaires de contrôle local pour les tumeurs avancées et précoces sans augmentation des effets secondaires tardifs. Ces résultats soutiennent les avantages cliniques potentiels de la CT-PDR et s'alignent sur les modèles radiobiologiques prédisant une fenêtre thérapeutique plus large.

La thèse explore également le potentiel de la CT-PDR pour améliorer le contrôle local chez un sous-groupe de patients atteints de CCLA sans augmenter le risque d'effets secondaires. Cependant, elle souligne également les limites du modèle linéaire quadratique, qui peuvent entraîner des inexactitudes dans l'analyse des résultats. De plus, la réalisation d'un essai clinique randomisé pour fournir des preuves solides sur les avantages de la PDR reste un défi en raison de la taille d'échantillon requise et de la faible disponibilité de la modalité PDR.

Pour comprendre pleinement les avantages potentiels de la CT-PDR et intégrer ces résultats dans la pratique clinique, des recherches supplémentaires sur le modèle linéaire quadratique et la radiobiologie sont essentielles. Ces résultats contribueront à maintenir le rôle de la PDR dans le paysage de la curiethérapie et à améliorer potentiellement le pronostic des patients atteints de CCLA.

Titre : Explorer le Potentiel de la Curiethérapie à Débit de Dose Pulsé : Fondements Radiobiologiques et Implications Cliniques dans le Cancer du Col Utérin Localement Avancé

Mots clés : Curiethérapie, Radiobiologie, Débit de dose.

Résumé : L'impact du débit de dose a été le principal axe de recherche en radiobiologie pour les traitements par curiethérapie, tandis que les données sur d'autres facteurs d'influence restent limitées. Les études précliniques ont établi la supériorité radiobiologique théorique de la curiethérapie à débit de dose pulsé (PDR) et bas débit de dose par rapport au haut débit de dose, et des modèles biologiques et prédictifs ont été développés pour aider à déterminer les modalités de curiethérapie optimales pour des situations spécifiques.

Malgré les promesses de la curiethérapie PDR sous tendues par les données précliniques, il existe un manque notable de preuves cliniques pour étayer ces résultats. Une méta-analyse sur des patients atteints de cancer du canal anal est présentée, révélant des informations concordantes sur les avantages cliniques potentiels de la curiethérapie PDR.

Cela inclut la possibilité de délivrer des doses plus élevées et d'obtenir, grâce à l'escalade de dose sur des maladies localement avancées, des niveaux de contrôle local similaires à ceux des tumeurs plus localisées, sans augmentation des effets secondaires.

Enfin, le potentiel de la curiethérapie PDR pour améliorer le contrôle local dans une fraction de patients atteints de cancer du col utérin à un stade localement avancé, sans augmenter le risque d'effets secondaires, est exploré. Des facteurs ont été identifiés pour déterminer quels patients pourraient en bénéficier. Ces résultats permettent également d'évaluer les futurs axes de recherche à privilégier.

Title : Exploring the Potential of Pulsed Dose Rate Brachytherapy: Radiobiological Foundations and Clinical Implications in Locally Advanced Cervical Cancer

Keywords : Brachytherapy, Radiobiology, Dose Rate

Abstract : The dose/rate effect has been the main focus of radiobiological research in brachytherapy treatments, while data on other influencing factors remain limited. Preclinical studies have established the theoretical radiobiological superiority of pulsed dose rate (PDR) and low-dose rate over high-dose rate brachytherapy, and biological and predictive models have been developed to set up optimal brachytherapy modalities for specific situations.

Despite the promise of PDR brachytherapy regarding preclinical studies, there is a noticeable lack of clinical evidence to support these findings. A meta-analysis of patients with anal canal cancer is presented, uncovering consistent insights into the potential clinical advantages of PDR.

These benefits include the capacity to administer higher radiation doses and attain comparable levels of local control in locally advanced diseases, through dose escalation, as seen in more localized tumors, without increasing side effects.

Finally, the potential of PDR brachytherapy in improving local control in a fraction of locally advanced cervical cancer patients, without increasing the risk of side effects, is explored. Factors have been identified to determine which patients might benefit from PDR brachytherapy, and insights on how to advance in this area are discussed.