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Évolution au cours du temps des contrôles qualité des essais cliniques en radiothérapie

Gaëlle Le Quellenec

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pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

DES d'ONCOLOGIE RADIOTHERAPIE

par

Gaëlle LE QUELLENEC

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**ÉVOLUTION AU COURS DU TEMPS DES CONTROLES QUALITE DES ESSAIS
CLINIQUES EN RADIOTHERAPIE, UNE REVUE SYSTEMATIQUE DE LA LITTERATURE**

Président : Madame le Professeur Juliette THARIAT

Directeur de thèse : Monsieur le Professeur Stéphane SUPLOT

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CONTEXTE

Définition

Le contrôle qualité dans les essais cliniques impliquant la radiothérapie est un processus visant à évaluer la conformité du plan de radiothérapie. Ces processus couvrent tous les aspects de la radiothérapie allant du contrôle de la délinéation, de la dosimétrie, des infrastructures ou de la précision du traitement sous l'accélérateur de traitement (1). Ce plan de traitement est évalué selon le protocole de l'essai clinique qui définit les directives et les déviations acceptables ou non du plan du traitement.

Il existe une variabilité inter- et intra-individuelle importante dans la préparation des plans de traitement dans ou en dehors des essais cliniques (2). Il s'agit donc d'une étude essentielle pour les essais cliniques pour garantir que la qualité du plan de radiothérapie est suffisante pour ne pas compromettre les résultats de l'étude que ce soit pour le contrôle tumoral, la survie ou la toxicité. Elle est également importante pour que les différents bras de traitement des essais cliniques soient comparés de manière fiable et reproductible.

A plus grande échelle, en réduisant les déviations aux protocoles, le contrôle qualité permet de détecter les erreurs systématiques dans la pratique clinique et réduit les incompréhensions potentielles des recommandations (3). Ceci contribue à améliorer les pratiques de radiothérapie dans les centres pour tous les patients, même non inclus dans un essai clinique. Le retour d'avis lors des processus d'évaluation par les pairs des plans de traitement permet une amélioration de la courbe d'apprentissage pour chaque investigateur participant aux essais cliniques.

Historique

Les différents groupes coopératifs de radiothérapie ont mis en place des procédures de contrôle qualité dans leurs protocoles d'essai clinique depuis les années 80 (3-5). C'est l'exemple de l'Organisation Européenne pour la Recherche et le Traitement du Cancer (European Organization for the Research and Treatment of Cancer EORTC) qui a publié

des recommandations de bonnes pratiques de rédaction de protocole d'essai clinique incluant des contrôles qualité en 1995 (6).

En 2010, le groupe d'harmonisation global des essais cliniques (Global Clinical Trials RTQA Harmonization Group GHG) a été créé dans le but d'harmoniser les contrôles qualités de tous types dans les essais cliniques impliquant la radiothérapie (7). Depuis lors, les contrôles qualité devraient devenir de plus en plus systématique, avec toutefois des variations dans leur caractéristiques rétrospectif ou prospectif et les critères (contours, dose, etc.) soumis à évaluation.

A la même période, un groupe d'étude organisé par l'institut national du cancer (NCI National Cancer Institute) à Rockville aux Etats Unis en 2010, évaluait les bonnes pratiques de contrôle qualité et recommandait leur réalisation dans tous les essais cliniques incluant un traitement par radiothérapie, avec des caractéristiques variables en fonction de l'objectif de l'étude (3).

A l'instar des Etats Unis, l'EORTC publie régulièrement des recommandations sur les bonnes pratiques en radiothérapie et notamment l'implémentation d'un contrôle qualité minimal pour tous les essais cliniques (8).

Impact sur la clinique

De nombreuses études ont montré que les écarts par rapport au protocole sont associés à une diminution de la survie globale et des objectifs secondaires dans les essais cliniques (9-12).

L'un des exemples les plus connus est celui du TROG 02-02, publié en 2010. En effet, dans cette étude évaluant l'ajout d'un radiosensibilisant, la tirapazamine, à un traitement de radiochimiothérapie pour les carcinomes épidermoïdes ORL, la survie globale à 2 ans n'était pas améliorée dans le bras expérimental avec 66,2% contre 65,7% dans le bras contrôle (13). Une analyse rétrospective de la qualité des plans de traitement était prévue dans le protocole. Celle-ci retrouvait 25,4% des plans avec au moins une déviation sur un critère étudié. L'analyse, *a posteriori*, des résultats en fonction des déviations retrouvait une tendance à une amélioration du contrôle locorégional dans le bras expérimental (79%

vs 75% à 2 ans) pour les patients traités sans aucune déviation (14). Ainsi, la qualité de la RT a pu affecter les résultats de l'essai clinique au point que le groupe de traitement expérimental a été jugé non supérieur au groupe contrôle, la qualité de la RT jouant le rôle d'un facteur de confusion.

De la même manière, en 2013, Ohri et al ont effectué une méta-analyse portant sur l'impact clinique des déviations au protocole de radiothérapie dans les essais cliniques (15). Parmi les 8 articles étudiés, la fréquence des déviations au protocole était de 8 à 71% avec une médiane de 32%. Les déviations aux plans de traitement impactaient de manière statistiquement significative la survie globale ainsi que les objectifs secondaires des études avec une augmentation de 75% du risque de traitement inefficace ou de mortalité. Plus récemment, une méta-analyse portant sur 5 essais cliniques publiés depuis 2005 a évalué plus précisément les déviations concernant la délinéation des volumes cibles et retrouvait un impact de celles-ci sur la survie globale et la toxicité du traitement (16).

Différents types de RTQA

Il existe plusieurs types de contrôle qualité avec différents niveaux d'exigences et de complexité. En 2014, le GHG a listé les 27 procédures de contrôle qualité retrouvées dans la littérature afin d'en réduire le nombre à 10 procédures harmonisées (17). Parmi celles-ci, nous pouvons retrouver :

- Facility questionnaire : questionnaire sur les installations de chaque centre participant à l'étude, leurs charges de travail, équipements et procédures.
- Beam Output Audit : mesure du rendement des faisceaux de traitement dans des conditions de référence
- Benchmark case (BC) : évaluation sur un cas de référence de la délinéation et de la planification
- Dummy run (DR) : évaluation sur les données d'un cas interne à chaque centre de la délinéation ou de la planification
- Individual Case Review (ICR) : évaluation rétrospective ou prospective du plan de traitement et de la délinéation des patients inclus dans l'étude
- Complex dosimetry check ou End-To-End test : évaluation dosimétrique des plans de traitement à l'aide d'un fantôme fourni un groupe d'audit dosimétrique.

L'EORTC a référencé différents niveaux de contrôle qualité du moins exigeant au plus exigeant (5):

- Niveau 1 : Facility questionnaire et Beam Output Audit
- Niveau 2 : niveau 1 + BC ou DR
- Niveau 3 : niveau 2 + ICR limité sur une partie des patients inclus (premiers patients inclus dans chaque centre ou pourcentage de patients inclus)
- Niveau 4 : niveau 2 + ICR extensif sur tous les patients inclus
- Niveau 5 : niveau 4 + End-to-End test.

La faisabilité d'un contrôle qualité exhaustif et prospectif dépend des installations pour la recherche clinique dans chaque centre, de la disponibilité des experts et du nombre de patients inclus. Une analyse coût-efficacité des contrôles qualité des essais cliniques a retrouvé des résultats en faveur de l'augmentation du niveau d'exigence du contrôle qualité avec une augmentation du coût compensée par les résultats de survie et de qualité de vie des patients, ceci était d'autant plus important entre le niveau 2 et le niveau 4 de contrôle qualité (18). Toutefois, il n'existe pas, à l'heure actuelle, de recommandation sur le type de contrôle qualité à réaliser en fonction du type d'essai clinique (phase, nombre de patients inclus, objectif de l'étude...).

Justificatif de l'étude

Les contrôles qualité dans les essais cliniques impliquant la radiothérapie sont donc un processus très exigeant, nécessitant du temps, des ressources humaines et financières, ainsi qu'une logistique technique contraignante. Ces contraintes ne doivent pas retarder l'initiation de la radiothérapie pour les patients inclus. La question du contrôle qualité est opportune alors que les technologies de traitement sont de plus en plus avancées et complexes et que le nombre de patients atteints de cancer continue d'augmenter. Par ailleurs, les outils de contrôle qualité s'améliorent grâce aux progrès des plateformes numériques et de l'intelligence artificielle, y compris les approches de Machine et Deep Learning.

Cependant, l'arrivée de ces nouvelles technologies n'a pas semblé rendre plus systématique les procédures de contrôle qualité ni leur publication dans la littérature (19,20).

Connaissant ces contraintes et tendances récentes, nous avons entrepris une analyse systématique de la littérature afin d'évaluer au cours du temps la réalisation des procédures de contrôle qualité dans les essais cliniques impliquant la radiothérapie ainsi que les paramètres influençant le type de contrôle qualité.

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ARTICLE

Radiotherapy Quality Assurance over the course of time, a systematic literature review

Gaëlle Le Quellenec¹ MD ; Tanguy Perennec¹ MD ; Juliette Thariat² MD PhD ; Stéphane Supiot¹ MD PhD

¹Department of Radiation Oncology, Institut de Cancérologie de l'Ouest, Nantes, France

²Department of Radiation Oncology, Centre François Baclesse, Caen, France

Key-words

Radiotherapy quality assurance; benchmark case; individual case review

Key points

Question: How do the radiotherapy quality assurance procedures in clinical trials evolve over time in a climate of increasing advanced radiation technologies?

Findings: In this overview of trials published in PubMed between 1988 and 2022, 130 studies were found to perform an RTQA and only 96 of them to publish their results. Compared to studies registered on Clinicaltrials.gov database, only 1.14% performed an RTQA with no significant increasing trend over time.

Meaning: This study highlights the few numbers of trials performing RTQA and the warrant harmonization in these procedure.

Abstract

Importance

Radiotherapy quality assurance (RTQA) is a systematic process by which a RT plan conformity is analysed with respect to RT planning guidelines in the trial protocol and is an essential step in clinical trials to ensure the reliability of the trial results. In the past, some studies have shown that protocol deviations significantly affect the clinical trial outcome and decrease overall survival.

Objective : To assess RTQA trends over time and parameters influencing the type of RTQA.

Design, settings, and participants

This is an overview of trials published in PubMed between 1988 and 2022 which performed and published their RTQA results. A research was also performed on ClinicalTrial.gov database to find the actual number of clinical trials using radiotherapy as a treatment.

Main outcomes and measures

Characteristics of clinical trials and propensity to conduct RTQA were overviewed over the time. The trends toward more systematic and prospective RTQA were assessed.

Results

Among 663 articles found on PubMed, 130 studies were selected as conducting RTQA between 1988 and 2022. Of these studies, 96 trials published qualitative or quantitative analysis. During the same period, compared to registered trials on Clinicaltrial.gov database 1.15% and 0.85% of trials performed and published a RTQA respectively with no significant trend over time. Seventy-three trials (58%) performed a benchmark case or dummy run, 93 (73.8%) an individual case review and 24 (18,9%) an End-to-End audit, with an upward trend towards benchmark case or dummy run. A higher proportion of prospective RTQA was retrieved over time (BC/DR : 33.3% during 1988-1999 vs 100% during 2016-2022; ICR: 16.7% during 1988-1999 vs 50% during 2016-2022).

Conclusions and relevance

RT quality assurance is important to ensure RT plan quality among clinical trials. This study highlights the few numbers of trials performing RTQA and even fewer publishing

them. No significant increase over time was retrieved while advanced RT techniques steadily grows. However, more complete RTQA procedures were showed over time. Types of RTQA vary substantially over the time and more analysis should be performed to assess the most adequate and reliable RT plan quality assurance.

Abbreviations

AI: artificial intelligence

BC/DR: benchmark case / dummy run

DL: deep learning

EORTC: European Organization for. Research and Treatment of Cancer

FQ: facility questionnaire

GHG: Global Clinical Trials RTQA Harmonization Group

GI: gastro-intestinal

HNSCC: head and neck squamous cell carcinoma

ICR: individual case review

IMRT: intensity modulated radiation therapy

ML: machine learning

OAR: organ at risk

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

RT: radiotherapy

RTQA: radiotherapy quality assurance

SBRT: stereotactic body radiotherapy

TROG: Trans Tasman Radiation Oncology Group

Introduction

In clinical trials involving radiotherapy (RT), quality assurance (RTQA) is a systematic process by which RT plan (or some aspects of it) conformity is analysed with respect to RT planning guidelines in the trial protocol and defined as deviations. RTQA is an essential step in clinical trials to ensure that quality of RT plans is on the one hand sufficient not to compromise outcomes (tumor control and toxicities), and on the other hand equally distributed across clinical trial arms to enable reliable comparisons. It may also contribute to improve RT plan quality for the in-trial patients, and outside the context of clinical trials as part of the learning curve and peer review process. Cooperative research groups have implemented RTQA procedures in their trial protocols since the 80's (1,2). In 2010, the Global Clinical Trials RTQA Harmonization Group (GHG) was created with the main objective to harmonize RTQA (3). Since then, RTQA is expected to become increasingly systematic in clinical trials with, however, variations in their retrospective or prospective timing and criteria (contours, dose, *etc*) subjected to quality assurance.

Multiple studies have shown that protocol deviations are associated with poorer overall survival and secondary outcomes in clinical trials (4–7). As in one of the most well-known example, in TROG 02-02 RT quality may affect clinical trial outcome to the point where the experimental treatment arm would be assessed as not superior to the standard arm due to RT quality playing the role of a confounding factor (8). Likewise, Ohri showed a 75% increased risk of ineffective treatment or mortality (9).

However, RTQA is a very demanding process; it is time-consuming, it requires human and financial resources and technical logistics. These strong constraints should not result in delayed patient RT initiation. Adaptations have been made across trials with different levels of increasing requirement, such as Facility Questionnaire (FQ), Dummy Run (DR), or Individual Case Review (ICR) for various proportions of in-trial patients. The feasibility of comprehensive and prospective RTQA is however dependent on patient accrual rate, center clinical research facilities, RTQA expert availability, urge to treat the patients, *etc*. Retrospective RTQA, Benchmark case and end-to-end tests are less demanding RTQA modalities but have less potential to improve individual patient prognosis (10). RTQA

may therefore vary substantially but the question is very timely as the number of cancer patients continues to increase while RTQA tools improve with advances in digital platforms, and Artificial Intelligence (AI), including Machine Learning (ML) and Deep Learning (DL) approaches.

Knowing these constraints and trends, we undertook a systematic literature review and assessed RTQA trends over time and parameters influencing the type of RTQA.

Methods

Selection of trials

We conducted research using PubMed on radiotherapy and quality assurance in clinical trials. On PubMed, the following algorithm was used: (("radiotherapy"[MeSH Terms]) OR ("radiation therapy"[Title/Abstract])) AND (("dummy"[All Fields]) OR ("Quality Assurance"[All Fields]) OR ("RTQA" [All Fields]) OR ("Individual Case Review"[All Fields])). We did not apply any filter for publication date. We restricted our selection to interventional studies published in English or French. Duplicate articles were excluded. If several articles about the same trial were found, we chose the most recent or the most detailed one and used the others to complete the information.

Then, we searched the clinical studies registered on ClinicalTrials.gov (11). We restricted our research to interventional studies with radiotherapy as intervention. The number of clinical trials opened per year was recorded.

Data extraction

Data extraction was conducted by one investigator (GLQ) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (12). In case of uncertainty, the investigator extracting data referred to the other investigators for agreement. For each study, the following information were extracted: author, year of publication, name and phase of the clinical trial, country or cooperative group investigator, number of patient enrolled, number of centers, organ treated, RT techniques and characteristics, RTQA procedures and primary outcomes of the study. Articles that detailed RTQA techniques but not RTQA results of a clinical trial were excluded from the detailed analysis of BC/DR and ICR characteristics.

Naming conventions about RTQA procedures were those defined by the GHG (10). In brief, benchmark cases (BC) were defined as full RT planning or delineation test in one CT scan provided to centers by the RTQA team, and dummy run (DR) as a similar process on a CT scan from centers' in-house patients. We analyzed BC and DR together. Individual case reviews (ICR) were reviews of actual treatment plans of in-trial patients. In addition, End-to-End audit were defined as beam output audit and entire treatment dosimetry check.

Evolution over time of data was assessed through four periods separated by three important date: 2000, 2010 and 2016 corresponding to the emergence of 3D, publication of the pivotal TROG 02.02 RTQA article, and widespread of extracranial stereotactic body RT (SBRT) respectively (13–15)

Statistical analysis

Statistical analysis was performed with Python 3.8.10. The results for categorical variables are expressed as absolute numbers and percentages, and the association between time groups is tested with a chi-square test. The results for continuous variables are expressed as median (interquartile range), and the association between groups is tested using ANOVA. Tests associated with a p -value under 0.05 were considered statistically significant. As a systematic review, no statistical analysis was performed on the overall variables.

Results

Selection of trials

Our search yielded 663 articles (637 on PubMed and 26 referred articles) from 1988 to December 2022. Based on titles and abstracts, 502 articles were excluded, leading to 162 articles referring to a RTQA procedure or result (**Figure 1**). After reading these 162 articles, 32 articles were found to be duplicate articles of the same trial. Of the 130 trials that reported having carried out an RTQA, 96 trials published their results (73.8%). These trials are listed in **Table 1**.

RTQA procedures among trials

On the same period of time, 11369 interventional studies with RT intervention were registered on ClinicalTrial.gov. Based on that denominator, 1.14% and 0.84% of trials performed and published their RTQA respectively. As illustrated **Figure 2A**, the absolute number of performed RTQA increased with time to up to 25 trials during the period 2015-2017. However, based on trial number in Clinicaltrial.gov database, the proportion of trials which carried out an RTQA decrease until 2003 to stabilize then. (**Figure 2B**).

RTQA trends over time by parameters

Trial characteristics and time trends are presented in **Table 2**. Most of the trials were not international, with no clear change over time. Most of the studies were performed in Europe (n= 58, 44.6%), followed by the US (n= 25, 19.2%). A new trend for intercontinental studies was observed since 2016 corresponding to 23.5% (n=12) of studies performed during the last 2016-2022 period. Across all time periods, the vast majority of trials evaluated RT as primary intervention (n=93, 71.5%). A significant increase in the number of trials conducted for patients with gastrointestinal (GI) cancer was observed while the proportion of trials conducted for patients with prostate or breast cancer decreased during the last 2016-2022 period.

RTQA results were published before publication of the study results in 69 cases (78.4%). Half of the studies achieved their primary endpoint (n=55, 67.1%); 21 studies were still recruiting, and 6 studies had been closed before completion.

Seventy-three trials (58%) performed a BC/DR, 93 (73.8%) an ICR and 24 (18.9%) an End-to-End audit (**Figure 3**); of these 72.6% (n=53), 69.9% (n=65) and 66.7% (n=16) were published respectively.

BC/DR trends over time

Table 3 presents the characteristics of the 53 trials that performed and published 52 BC and 1 DR. Those were increasingly performed in a prospective way from 33.3% during the first 1988-1999 period to 100% during the latest. Credentialling procedure increased from 33.3% to 86.7%. One patient case was performed in 62.3% of the trials (n=33) with no major evolution over time. A higher proportion of centers that participate to the planned RTQA procedure was retrieved during the last period (median: 100%, IQ: 100-110%) but some centers participated to the BC/DR without enrolling patients after study opening in 9 trials (17%).

Delineation and dosimetry of the BC/DR were analyzed in 28.6%, 25.7% and 40% by a group of radiation oncologists and physicists (n=10), only one or more radiation oncologists (n=9) and another group (n=14) (RTQA team without precision (n=7), one or two reviewers without precision (n=6), and a study meeting (n=1)) respectively. No clear time trend was found. Analyses were more likely objective using geometrical tools (e.g. Dice coefficient, Jacard index, Hausdorf distance) over time (1988-1999: 33.3%; 2016-2022: 63.2%).

ICR trends over time

Sixty trials (46%) performed and published an ICR which characteristics are showed **Table 4**. Only 35.1% of the ICR were carried out prospectively with a trend towards an increasing proportion of prospective ICR (1988-1999: 12.5%; 2016-2022: 50%, p= 0.136) (**Figure 4**). The proportion of centers participating to the ICR was high with a median overall of 100% (IQ: 90-100%). Stable over time, ICR RTQA were performed on a median of 80% of included patients (IQ: 30-100%). A decrease in the number of ICR planned in

the studies' protocols was observed over time; with notably a decrease in the number of trials requiring an ICR for all patients from 75% to 50% in the periods 1988-1999 and 2016-2022 respectively.

Delineation and dosimetry of the ICR were subjectively analyzed in 37.2%, 23.3% and 37.2% by one or more radiation oncologists (n=16), a group of radiation oncologists and physicists (n=10), and another group (n=16) (RTQA team without precision (n=9), one or two reviewers without precision (n=6), and investigation center (n=3)) respectively, with no major change over time.

Discussion

RT quality assurance is a very important procedure to ensure RT plan quality among clinical trials. However, the actual number of trials performing RTQA is very limited to 1.14%. Surprisingly, after the publication of the TROG 02.02 results and the foundation of the GHG in 2010, while an increase in the RTQA procedures would have been expected, we observed a stagnation in the proportion of RTQA planned in study protocols around 1%.

As previously observed, RTQA is underreported and this does not improve over time (16). Only two thirds of trials published their RTQA results; 73.7% representing 0.84% of all trials registered in ClinicalTrial.gov. This is, however, more than other trials reported in the literature focusing on phase III randomized trial, hence in Corrigan's review, none of the 42 trials registered in ClinicalTrial.gov published their RTQA results (17). Similarly, only 11% and 27% of trials on lymphoma and prostate cancer patients respectively published their results (16,18). The higher proportion of published RTQA in our review might be explained with the higher proportion of phase I/II study which is increasing over time from 37.5% in the 2000-2009 period to 52.9% during 2016-2022. Hence, early phase trials are probably more likely to publish their RTQA results than phase III trials. A stable 75% of trials performing RTQA published their results before study results, allowing the readers an assessment of the study reliability.

Some trial types were found to more likely perform RTQA. The majority of studies that carried out an RTQA was performed in a single country (65.9%). A higher proportion of European studies was found to perform RTQA (44.6%), whereas previous audits observed that 45.5% of RT trials are made in USA (19,20). This may be due to a high proportion of trials conducted by European Organisation for Research and Treatment of Cancer (EORTC) (n=13 ; 10%) which has a long-standing policy of quality control for their trials (2). Despite the unfortunate story of TROG 02.02 conducted in Australia, few studies were carried out in Oceania which may be explained by a potential smaller number of conducted or published trials or a tendency to participate to intercontinental studies. At the opposite, the number of Asian trials performing an RTQA increased over time so did the number of trials in Asia (19,20). Cancer types studied more frequently in the trials performing RTQA were gastro-intestinal, prostate and lung cancers (Table 2) which is consistent with the oncological practice and studies conducted with radiotherapy as the

primary treatment modality (19). However, during the last 2016-2022 period, we observed a marked trend towards an increase in the number of studies performing RTQA in gastro-intestinal, especially pancreatic ($n=8/51$), and metastatic cancers; whereas a downward trend in prostate and head and neck cancers studies. These trends do not follow the evolution of the type of RT clinical trials studied by Chen et al, who found more studies on head and neck, cerebral and gastrointestinal cancers over the 2017-2022 period (20). The long experience in prostate or head and neck treatments without recent changes in delineation guidelines may have led to a decrease in RTQA procedure. Finally, 90% of studies performing RTQA were non industry sponsored (Table 2), which is in line with the higher proportion of trials which assessed a RT treatment/modality and the current practices in RT clinical trials (16,19).

ICR were more frequently performed than BC/DR and End-to-End with an upward trend in BC/DR since 2015. Several improvements were made from 1988-1999 to 2016-2022. First, a significant increase in the proportion of centres participating to these RTQA was showed considering BC/DR from 40% to 100% for the first and last period respectively. The median proportion of participating centres was stable to 100% over time considering ICR. A large upward trend in credentialing procedure was noticed from one-third over the first 1988-1999 period to 86.7% over the last period, meanwhile advanced RT techniques have become more complex and been implemented in some centres as part of at least 2 trials (21,22). This trend was previously described by Corrigan et al, albeit less significant, who showed that 19 out of 42 phase III clinical trials (45%) required credentialing to allow institutions participation, including 11 (58%) trials that used advanced RT techniques (17). Finally, improvement in the number of trials performing prospective ICR before patients treatment begins was retrieved, yet to only 50% of trials over the last period despite recommendations previously published to perform ICR as early as possible to ensure good compliance of the treatment for each patient (18).

Over time, RT techniques and practices significantly varied leading to an increased complexity but we noted a stagnation in the number of RTQA procedures during the last decades, with ongoing efforts to improve their quality. As complex advanced RT techniques appeared and spread, a decrease in the proportion of trials performing RTQA is observed. The majority of RTQA was carried out for 3D RT techniques (BC/DR: 50%; ICR: 43.9%). Interestingly, physicists play an increasingly important role in quality analysis, while RT plans and their compliance to protocol are becoming more complex to

assess, as previously suggested (17). While geometrical tools for comparing target volumes have been known for over a hundred years and increasingly used since the 2000s (23,24), only 54.7% of DR/BC quantitatively analysed target and/or OAR volumes; albeit with a slight increase in their use over the last 2016-2022 period (63.2%). As for the ICR, geometric indexes were found to be used since 2013 (25), with only 5 out of 60 studies performing an objective analysis. OAR delineation analysis decreased over time, slightly more markedly for ICR than for BC/DR, possibly due to publications of OAR delineation guidelines and the assumption that the learning curve has been reached, without further deviation, or to the development of automatic OAR delineation software. Moreover, over the 53 trials that performed and published their BC/DR procedure, we found a slight decrease in the number of evaluated cases which may be explained by investigators' intent to reduce the workload for each centre, given the increasing time required to prepare a complete RT plan for a patient. A trend for a decrease in the number of ICR planned in the protocols was found. Hence, the number of trials whose protocol required ICR for all patients dropped from 75% in 1988-1999 to 50% in 2016-2022. However the proportion of ICR based on the number of patients included was 80% during the last 2016-2022 period due to extra ICR planned randomly during the inclusion period for trials whose protocol required ICR for the first patients (26–28).

Only few trials performed End-to-End audit with no significant evolution over time. This may be due to a time-consuming and costly procedure that needs to be anticipated in the protocol. However, our Medline research did not include End-to-End terms which may have led to selection bias. For this reason, data from studies that performed End-to-End audit were not analysed in this article.

One of the limitation of this study is that several clinical trials that reported having performed RTQA did not publish the results. This lack of data was higher for the last 2016-2022 period (BC/DR 34.7%; ICR 28.6%; End-to-End 10.2%) while some trials were still opened (n=12); which may result to a tendency not to show the RTQA latest evolution of currently open clinical trials. Secondly, a time lag may occur between registration in Clinicaltrial.gov and publication of the study. This time lag may vary according to the type of study; e.g. a study conducted on prostate or breast cancer often includes more patients with longer follow-up and will therefore take longer to publish the results. Only 70% of clinical trials are registered into Clinicaltrial.gov (19). However, the choice of using only this registry was made to avoid redundancies as several trials were simultaneously

recorded in different registries. Hence, using data from multiple registries would have led to an even lower proportion of studies that performed an RTQA. Finally, some uncertainties or biases may be inherent in the RTQA procedure itself. Indeed, we did not know whether the procedures were planned *a priori* in the statistical analysis of the trial, or whether the results of the RTQA impacted the trial procedure itself.

Conclusion

This study is the first overview of RTQA procedures among clinical trials. It highlights the few numbers of trials performing RTQA and even fewer publishing them. No significant increase over time was retrieved while advanced RT techniques steadily grows. However this study showed more complete RTQA procedures over time. Many kinds of RTQA were recorded with no harmonisation considering tools and analysis. Future studies are needed to characterize the different kind of tools depending on the trial type and to assess the most adequate and reliable RT plan quality assurance depending on trial aim and technology readiness level for trials investigating the impact of new RT techniques.

Conflicts of interest

None

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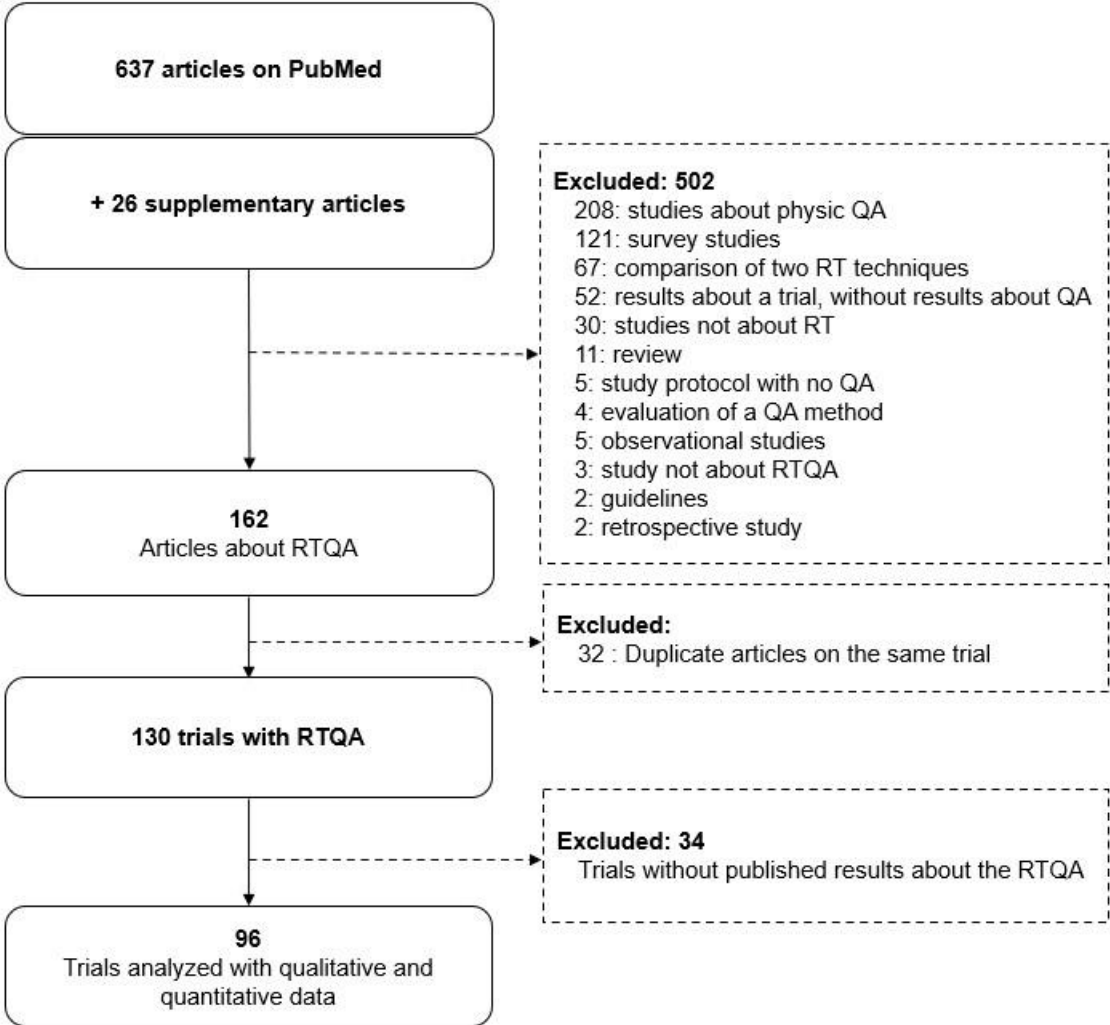
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Figures and Tables

Figure 1 Flowchart identifying trials that performed and published an RTQA

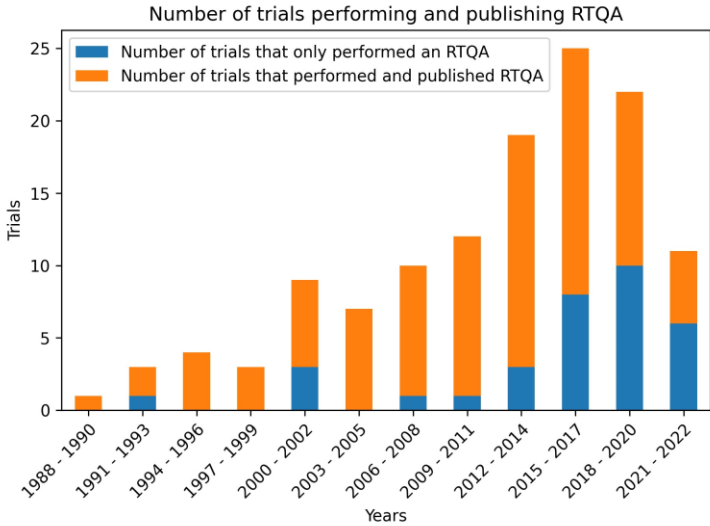


RT: radiotherapy; QA: quality assurance

Figure 2 Evolution of RTQA procedures over time

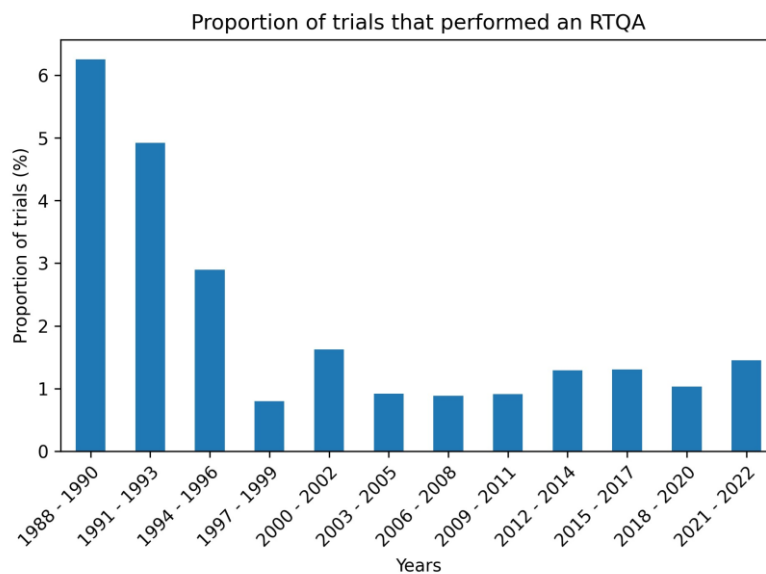
Number of trials published on PubMed that performed and published an RTQA (Figure 2A) and proportion of trials which performed an RTQA based on the number of clinical trials registered in ClinicalTrial.gov (Figure 2B).

Figure 2A.



Period	1988 - 1990	1991 - 1993	1994 - 1996	1997 - 1999	2000 - 2002	2003 - 2005	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2017	2018 - 2020	2021 - 2022
Trials performing RTQA	0	1	0	0	3	0	1	1	3	8	10	6
Trials publishing RTQA	1	2	4	3	6	7	9	11	16	17	12	5

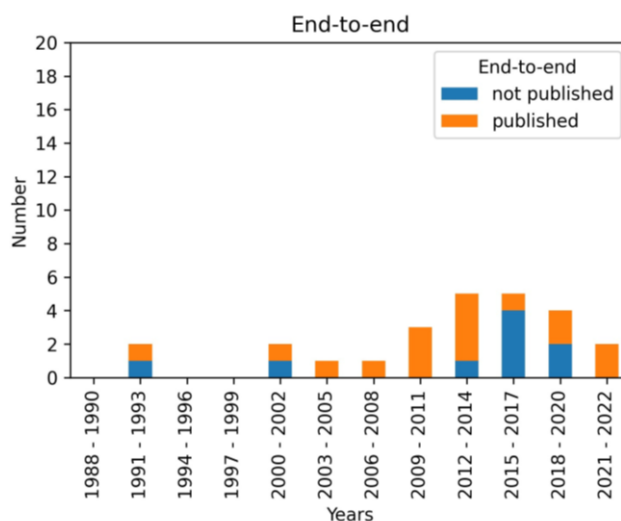
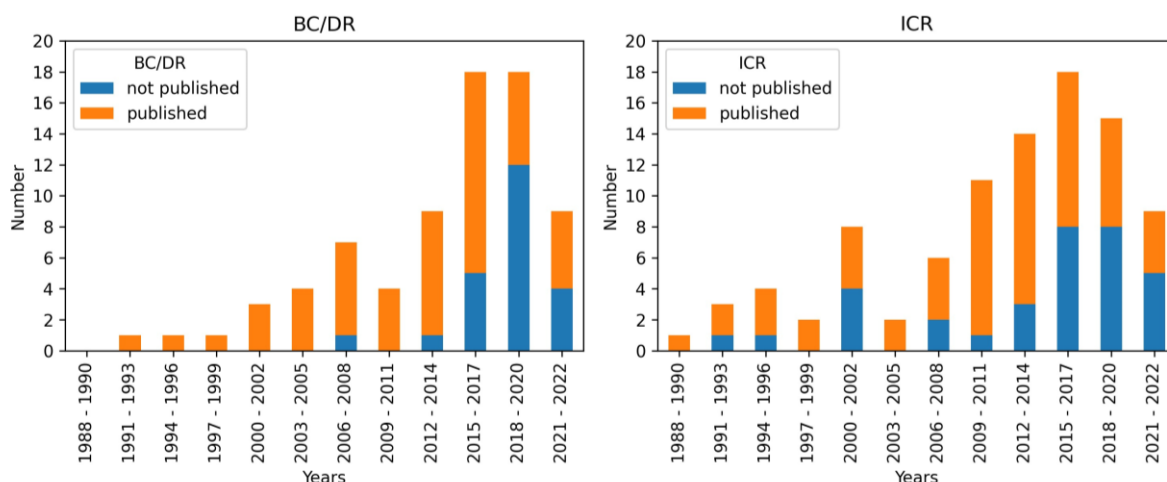
Figure 2B.



Period	1988 - 1990	1991 - 1993	1994 - 1996	1997 - 1999	2000 - 2002	2003 - 2005	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2017	2018 - 2020	2021 - 2022
Trials performing RTQA (%)	6.25	4.92	2.90	0.80	1.63	0.92	0.88	0.91	1.29	1.31	1.03	1.45

RTQA: radiotherapy quality assurance

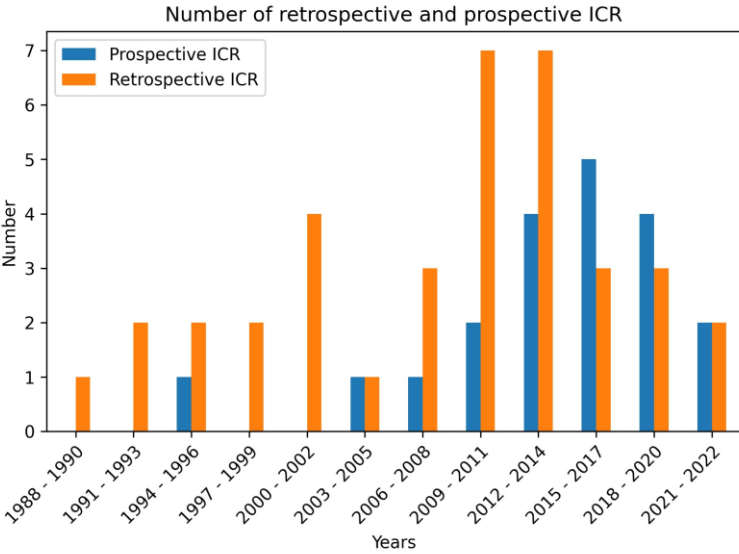
Figure 3 Evolution of RTQA types over time



Period		1988-1990	1991-1993	1994-1996	1997-1999	2000-2002	2003-2005	2006-2008	2009-2011	2012-2014	2015-2017	2018-2020	2021-2022
BC/DR	Published	0	1	1	1	3	4	6	4	8	13	6	5
	Non published	0	0	0	0	0	0	1	0	1	5	12	4
ICR	Published	1	2	3	2	4	2	4	10	11	10	7	4
	Non published	0	1	1	0	4	0	2	1	3	8	8	5
End-to-End	Published	0	1	0	0	1	1	1	3	4	1	2	2
	Non published	0	1	0	0	1	0	0	0	1	4	2	0

BC/DR: benchmark case/dummy run; ICR: individual case review; RTQA: radiotherapy quality assurance

Figure 4 Evolution of retrospective and prospective ICR



Period	1988 - 1990	1991 - 1993	1994 - 1996	1997 - 1999	2000 - 2002	2003 - 2005	2006 - 2008	2009 - 2011	2012 - 2014	2015 - 2017	2018 - 2020	2021 - 2022
Retrospective ICR	1	2	2	2	4	1	3	7	7	3	3	2
Prospective ICR	0	0	1	0	0	1	1	2	4	5	4	2

ICR : individual case review

Table 1 Summary of clinical trials included in this study

Study name	Year	Disease	Phase	Location	RT assessed	Primary endpoint achieved	RTQA published	BC/DR	ICR	End-to-end
International										
EORTC 22881/10882 (1,2)	1991	Breast	III	Europe	Yes	Yes	Yes	Yes	Yes	Yes
Intergroup protocol 86-47-5 1 (3)	1995	Rectum	III	Amérique	No	Yes	Yes	No	Yes	No
EORTC 22863 (4)	1995	Prostate	III	Europe	No	Yes	Yes	Yes	NP	No
EORTC 22931 (5)	1998	HNSCC	III	Europe	No	Yes	Yes	Yes	No	No
EORTC 22922/10925 (6,7)	2001	Breast	III	Europe	Yes	Yes	Yes	Yes	Yes	Yes
EORTC 22921 (8)	2002	Rectum	III	Europe	No	Yes	Yes	No	Yes	No
EORTC 22911 (9)	2002	Prostate	III	Europe	Yes	Yes	Yes	Yes	NP	No
CHARTWEL Bronchus (10)	2003	Lung carcinoma	III	Europe	Yes	No	Yes	No	No	Yes
EORTC AMAROS trial 10981/22023 (11)	2003	Breast	III	Europe	Yes	Yes	Yes	Yes	No	No
EORTC 22961 (12)	2004	Prostate	III	Europe	No	Yes	Yes	Yes	No	No
EORTC 22972-26991 (13)	2008	Glioma	III	Intercontinental	Yes	Other	Yes	Yes	No	No
EORTC 22991 (14)	2009	Prostate	III	Europe	No	Yes	Yes	Yes	Yes	Yes
EORTC 22033-26033 (15,16)	2010	Glioma	III	Intercontinental	Yes	No	Yes	Yes	Yes	No
SIOPEN Neuroblastoma HR (17)	2013	Pediatric tumor	III	Europe	No	Uk	Yes	No	Yes	No
EORTC 22043-30041 (18)	2013	Prostate	III	Europe	No	Other	Yes	Yes	No	No
PROFIT (19)	2013	Prostate	III	Intercontinental	Yes	Yes	Yes	NP	Yes	Yes
SAKK 09/10 (20)	2013	Prostate	III	Europe	Yes	No	Yes	Yes	NP	No
CONVERT (21-23)	2014	Lung carcinoma	III	Intercontinental	Yes	No	Yes	Yes	Yes	No
EORTC 22071-26071 (24)	2014	HNSCC	III	Europe	No	Other	Yes	Yes	No	Yes
TOPGEAR (25)	2015	Gastric cancer	III	Intercontinental	No	Other	No	No	NP	No
IAEA-HypoX (26)	2015	HNSCC	III	Intercontinental	No	Yes	Yes	No	Yes	No
AHOD0031 (27)	2015	Lymphoma	III	Intercontinental	Yes	Yes	Yes	No	Yes	No
EMBRACE (28)	2015	Cervical cancer	III	Intercontinental	Yes	Yes	Yes	Yes	No	No
EORTC 1219-DAHANCA 29 (29)	2017	HNSCC	III	Intercontinental	No	Uk	Yes	Yes	No	No
CATNON (30)	2018	Glioma	III	Intercontinental	No	Yes	Yes	No	Yes	Yes
PROCLAIM (31)	2018	Lung carcinoma	III	Intercontinental	No	No	Yes	No	Yes	No
EMBRACE II (32,33)	2019	Cervical cancer	III	Intercontinental	Yes	Uk	Yes	Yes	No	No
STRASS (34)	2020	Sarcoma	III	Intercontinental	Yes	Other	No	Yes	Yes	No
PORTEC 4a (35)	2021	Endometrial carcinoma	III	Europe	Yes	Other	Yes	Yes	Yes	No
SIOP PNET5 MB (36)	2021	Pediatric tumor	III	Europe	Yes	Other	Yes	No	Yes	No
SC24 (37)	2021	Bone metastasis	III	Intercontinental	Yes	Yes	No	No	Yes	No

LAP 07 (38)	2021	Pancreas	III	Intercontinental	Yes	No	Yes	No	Yes	No
POSNOG (39)	2021	Breast	III	Intercontinental	Yes	Other	No	NP	NP	No
PORTEC 3 (40)	2022	Endometrial carcinoma	III	Intercontinental	No	Yes	Yes	No	Yes	No
Scandinavian SBRT NSCLC (41)	2006	Lung carcinoma	II	Europe	Yes	Uk	Yes	Yes	No	No
EORTC 22042-26042 (42)	2013	Meningioma	II	Europe	Yes	Yes	Yes	Yes	Yes	No
PET Plan (43,44)	2015	Lung carcinoma	II	Europe	Yes	Uk	Yes	Yes	Yes	No
EORTC 22113-08113 Lungtech (45-47)	2016	Lung carcinoma	II	Europe	Yes	Uk	Yes	Yes	NP	Yes
TRENDY (48)	2017	Hepatocellular carcinoma	II	Europe	Yes	Other	Yes	Yes	Yes	No
STAR TreC (49)	2017	Rectum	II	Europe	No	Other	No	NP	No	No
Novalis Circle trial (50)	2020	Prostate	II	Europe	Yes	Yes	Yes	NP	Yes	No
RAIDER (51)	2020	Bladder	II	Intercontinental	Yes	Other	No	NP	NP	No
Coeliac plexus radiosurgery (52)	2022	Pancreas	II	Intercontinental	Yes	Other	No	NP	NP	No
PEACE V - STORM (53)	2022	Prostate	II	Intercontinental	Yes	Other	Yes	Yes	No	No
Non international										
Protocol 1000 (54)	1988	Prostate	III	USA	Yes	Yes	Yes	No	Yes	No
GBSG 1 (55)	1993	Breast	III	Germany	Yes	Uk	Yes	No	Yes	No
COMS (56)	1993	Choroidal melanoma	III	USA	Yes	Yes	No	No	NP	NP
CESS 86 (57)	1995	Pediatric tumor	III	Germany	Yes	Yes	Yes	No	Yes	No
HD4 (58)	1996	Lymphoma	III	Germany	Yes	Yes	Yes	No	Yes	No
HIT 91 (59)	1999	Pediatric tumor	III	Germany	No	Uk	Yes	No	Yes	No
TROG 91.01 (60)	1999	HNSCC	III	Australia	Yes	Uk	Yes	No	Yes	No
TROG 96.01 (61)	2000	Prostate	III	Australia	No	Yes	Yes	No	Yes	No
MRC RT-01 trial (62)	2000	Prostate	III	UK	Yes	Yes	Yes	Yes	NP	NP
IRS-IV (63)	2001	Pediatric tumor	III	USA	Yes	No	No	No	NP	No
POG trial 9404 (64)	2002	Pediatric tumor	III	USA	No	Yes	Yes	No	Yes	No
TROG 96.05 (65)	2003	Bone metastasis	III	Australia	Yes	No	Yes	No	Yes	No
AIROPROS 01-02 (66)	2003	Prostate	III	Italy	Yes	No	Yes	Yes	No	No
POG trial 9031 (67)	2006	Pediatric tumor	III	USA	Yes	Yes	Yes	No	Yes	No
CHOP regimen for NHL elderly patients (68)	2007	Lymphoma	III	Japan	No	Yes	Yes	No	Yes	No
ARTSCAN (69)	2008	HNSCC	III	Sweden	Yes	No	Yes	NP	Yes	No
Effect on radiotherapy on Plantar Fasciitis (70)	2008	Heel spur	III	Germany	Yes	Uk	No	No	NP	No
PARSPORT (71,72)	2009	HNSCC	III	UK	Yes	Yes	Yes	Yes	Yes	Yes
JAROG0401/JROSG04-2 (73)	2009	Cervical cancer	III	Japan	Yes	Yes	Yes	No	Yes	No
TROG 02.02 (74)	2010	HNSCC	III	Australia	No	No	Yes	No	Yes	No
ROSEL (75)	2011	Lung carcinoma	III	Netherland	Yes	Other	Yes	No	No	No
JCOG 0303 (76)	2012	Oesophagus	III	Japan	No	No	Yes	No	Yes	No
FAST trial (77)	2012	Breast	III	UK	Yes	Yes	Yes	No	Yes	No
RTOG 9704 (78)	2012	Pancreas	III	USA	No	No	Yes	No	Yes	No
TROG 03.04 RADAR (79,80)	2013	Prostate	III	Australia	No	Yes	Yes	Yes	Yes	Yes

RTOG 0126 (81)	2013	Prostate	III	USA	Yes	No	No	No	NP	NP
NIMRAD (82)	2014	HNSCC	III	UK	No	Uk	No	Uk	Uk	Uk
NEOSCOPE (83)	2015	Oesophagus	III	UK	No	Yes	No	NP	NP	No
RAVES (84,85)	2015	Prostate	III	Australia	Yes	No	Yes	Yes	Yes	No
KROG 08-06 (86,87)	2015	Breast	III	Japan	Yes	Uk	Yes	Yes	Yes	No
OCOG-LUSTRE (88)	2017	Lung carcinoma	III	Canada	Yes	Uk	Yes	Yes	NP	NP
PREOPANC (89)	2017	Pancreas	III	Netherland	Yes	Yes	Yes	Yes	No	No
TROG 09.02 (90)	2018	Lung carcinoma	III	Australia	Yes	Yes	Yes	Yes	No	No
WBRT-Mel (91)	2018	Brain metastasis	III	Australia	Yes	Uk	Yes	No	Yes	No
CHHiP (92)	2019	Prostate	III	UK	Yes	Yes	Yes	Yes	Yes	Yes
SPECTRO-GLIO (93)	2019	Glioma	III	France	Yes	Uk	No	NP	NP	NP
JCOG1402 (94)	2019	Cervical cancer	III	Japan	Yes	Uk	Yes	Yes	No	No
3JECROG P-01 (95)	2019	Oesophagus	III	China	Yes	Yes	No	NP	No	No
3JECROG P-02 (96)	2020	Oesophagus	III	China	No	Other	No	NP	No	No
STEREO OS (97)	2021	Bone metastasis	III	France	Yes	Other	No	NP	NP	No
ROCS (98)	2021	Oesophagus	III	UK	Yes	No	No	Uk	Uk	Uk
POTENTIAL (99,100)	2021	Breast	III	China	Yes	Other	No	NP	NP	NP
KROG 19-09 (101)	2022	Breast	III	Japan	Yes	Other	Yes	Yes	No	No
PulmonART (102)	2005	Lung carcinoma	II	Netherland	No	Uk	Yes	Yes	No	No
MSFOP-98 (103)	2005	Paediatric tumour	II	France	Yes	Yes	Yes	No	Yes	No
Dose escalation in pancreatic cancer (104)	2007	Pancreas	II	Japan	Yes	Yes	Yes	Yes	No	No
JCOG 0403 (105)	2007	Lung carcinoma	II	Japan	Yes	Yes	Yes	Yes	NP	Yes
RTOG 95-17 (106)	2007	Breast	II	USA	Yes	Yes	Yes	Yes	Yes	No
B9E-AY-S168 (107)	2008	Pancreas	II	Australia	No	Yes	Yes	Yes	No	No
JCOG 02-02 (108)	2009	Lung carcinoma	II	Japan	No	Uk	Yes	No	Yes	No
TROG 99.04 (109)	2009	Lymphoma	II	Australia	Yes	Other	Yes	No	Yes	No
RTOG 0411 (110)	2009	Pancreas	II	USA	No	No	Yes	No	Yes	No
RTOG 00-22 (111)	2010	HNSCC	II	USA	Yes	No	Yes	No	Yes	Yes
MIR study (112)	2011	Lymphoma	II	Germany	Yes	Yes	No	No	NP	No
RTOG 0116 and RTOG 0128 (113)	2012	Cervical cancer	II	USA	Yes	No	Yes	No	Yes	No
RTOG 0418 (114)	2012	Endometrial carcinoma	II	USA	No	Yes	No	No	NP	No
SCOPE 1 (115-117)	2012	Oesophagus	II	UK	No	No	Yes	Yes	No	No
RTOG 0529 (118)	2013	Anal carcinoma	II	USA	Yes	No	Yes	No	Yes	No
RTOG 0631 (119)	2014	Bone metastasis	II	USA	Yes	Yes	Yes	No	Yes	Yes
RTCMIENDOMETRE (120)	2014	Endometrial carcinoma	II	France	Yes	Yes	Yes	Yes	No	No
RTOG 0915 (121)	2015	Lung carcinoma	II	USA	Yes	Yes	No	No	NP	NP
RTOG 0933 (122)	2015	Brain metastasis	II	USA	Yes	Yes	Yes	Yes	Yes	No
SCALOP-1 (123)	2015	Pancreas	II	UK	No	No	Yes	Yes	Yes	No
AMC045 (124)	2017	Anal carcinoma	II	USA	No	No	Yes	No	Yes	No
E3205 (125)	2017	Anal carcinoma	II	USA	No	No	Yes	No	Yes	No

HIPPO (126)	2017	Brain metastasis	II	UK	Yes	Uk	Yes	Yes	No	No
KROG 12-02 (127)	2017	Hepatocellular carcinoma	II	Japan	Yes	Uk	Yes	Yes	No	No
CCTG PR15 (128)	2018	Prostate	II	Canada	Yes	Yes	Yes	No	Yes	No
KROG 17-06 (129)	2019	Brain metastasis	II	Japan	Yes	Other	Yes	Yes	No	No
PIVOTAL (130)	2019	Prostate	II	UK	Yes	Other	No	NP	NP	No
ADSCaN (131)	2019	Lung carcinoma	II	UK	Yes	Other	No	NP	NP	NP
SCALOP-2 (132)	2019	Pancreas	II	UK	Yes	Other	No	NP	NP	No
PRODIGE 26/CONCORDE (133)	2019	Oesophagus	II	France	Yes	No	Yes	Yes	No	No
HYBRID (134)	2020	Bladder	II	UK	Yes	Other	No	NP	NP	No
MASTERPLAN (135)	2021	Pancreas	II	Australia	Yes	Other	No	Uk	Uk	Uk
GORTEC 2014-14 (136)	2021	HNSCC	II	France	Yes	Other	Yes	Yes	No	No
POHIM-RT (137)	2021	Cervical cancer	II	Corea	Yes	Other	Yes	Yes	No	Yes
RTOG 9406 (138)	2000	Prostate	I	USA	Yes	Yes	No	No	NP	No
TROG 06.02 (139,140)	2009	Breast	I	Australia	Yes	Yes	Yes	Yes	Yes	No
Isotoxic IMRT NSCLC (141,142)	2016	Lung carcinoma	I	UK	Yes	Yes	No	NP	NP	NP
CHART-ED (143)	2016	Lung carcinoma	I	UK	Yes	Yes	No	NP	No	NP
A021101 (144)	2016	Pancreas	I	USA	No	Yes	No	No	NP	No
SPARC (145)	2017	Pancreas	I	UK	Yes	No	No	NP	NP	No
Cardiac sparing WLI (146)	2019	Paediatric tumour	I	USA	Yes	Yes	Yes	NP	Yes	No
RAVENTA (147)	2020	Ventricular tachycardia	I	Germany	Yes	Other	No	NP	NP	No
NIH 87-01 (148)	2002	Glioma	Uk	USA	Yes	No	No	Uk	Uk	Uk

BC/DR: benchmark case/dummy run; HNSCC: head and neck squamous cell carcinoma; ICR: individual case review; NP: non published; RT: radiotherapy; RTQA: radiotherapy quality assurance; Uk: unknown

Other: trials in progress or discontinued early

References in Appendix 1

Table 2 Characteristics over time of clinical trials that performed an RTQA

		<i>Missing</i>	Overall	1988-1999	2000-2009	2010-2015	2016-2022	<i>P-Value</i>
n			130	11	33	35	51	
Phase, n (%)	I/II	<i>1</i>	52 (40.3)		12 (37.5)	13 (37.1)	27 (52.9)	<i>0.011</i>
	III		77 (59.7)	11 (100.0)	20 (62.5)	22 (62.9)	24 (47.1)	
International, n (%)	yes	<i>1</i>	44 (34.1)	4 (36.4)	9 (28.1)	13 (37.1)	18 (35.3)	<i>0.871</i>
	no		85 (65.9)	7 (63.6)	23 (71.9)	22 (62.9)	33 (64.7)	
Sponsor, n (%)	Non industrial	<i>1</i>	116 (89.9)	10 (100.0)	31 (93.9)	29 (82.9)	46 (90.2)	<i>0.303</i>
	Industrial		13 (10.1)		2 (6.1)	6 (17.1)	5 (9.8)	
Location, n (%)	Europe	<i>0</i>	58 (44.6)	7 (63.6)	15 (45.5)	14 (40.0)	22 (43.1)	<i>0.027</i>
	America		25 (19.2)	3 (27.3)	6 (21.4)	10 (23.8)	6 (11.8)	
	Intercontinental		20 (15.4)		1 (3.0)	7 (20.0)	12 (23.5)	
	Asia		15 (11.5)		5 (15.2)	2 (5.7)	8 (15.7)	
	Oceania		12 (9.2)	1 (9.1)	5 (15.2)	3 (8.6)	3 (5.9)	
RT assessed, n (%)	yes	<i>0</i>	93 (71.5)	7 (63.6)	23 (69.7)	21 (60.0)	42 (82.4)	<i>0.132</i>
	no		37 (28.5)	4 (36.4)	10 (30.3)	14 (40.0)	9 (17.6)	
Disease, n (%)	GI	<i>0</i>	28 (21.5)	1 (9.1)	4 (12.1)	7 (20.0)	16 (31.4)	<i>0.570</i>
	Prostate		20 (15.4)	2 (18.2)	7 (21.2)	6 (17.1)	5 (9.8)	
	Lung carcinoma		16 (12.3)		5 (15.2)	4 (11.4)	7 (13.7)	
	Breast		11 (8.5)	2 (18.2)	4 (12.1)	2 (5.7)	3 (5.9)	
	HNSCC		11 (8.5)	2 (18.2)	2 (6.1)	5 (14.3)	2 (3.9)	
	Gynecological		10 (7.7)		1 (3.0)	4 (11.4)	5 (9.8)	
	Pediatric tumor		9 (6.9)	2 (18.2)	4 (12.1)	1 (2.9)	2 (3.9)	
	Metastasis		8 (6.2)		1 (3.0)	2 (5.7)	5 (9.8)	
	Cerebral		6 (4.6)	1 (9.1)	2 (6.1)	1 (2.9)	2 (3.9)	
	Lymphoma		5 (3.8)	1 (9.1)	2 (6.1)	2 (5.7)		
	Non Tumoral		3 (2.3)		1 (3.0)	1 (2.9)	1 (2.0)	
	Bladder		2 (1.5)				2 (3.9)	
	Sarcoma		1 (0.8)				1 (2.0)	
Publication before study results, n (%)¹	yes	<i>39</i>	69 (75.8)	7 (100.0)	21 (77.8)	20 (71.4)	21 (72.4)	<i>0.447</i>
	no		19 (20.9)		5 (18.5)	6 (21.4)	8 (27.6)	
	other		3 (3.3)		1 (3.7)	2 (7.1)		
Primary endpoint achieved, n (%)¹	yes	<i>20</i>	55 (50.0)	8 (100.0)	20 (69.0)	14 (45.2)	13 (31.0)	<i>0.060</i>
	no		27 (24.5)		7 (24.1)	13 (41.9)	7 (16.7)	
	other		28 (25.5)		2 (6.9)	4 (12.9)	22 (52.4)	

BC/DR : benchmark case/dummy run; GI: gastro-intestinal; HNSCC: head and neck squamous cell carcinoma; ICR: individual case review; RT: radiotherapy

Other: trials in progress or discontinued early

¹ : Statistical analysis performed only with the trials that published their study results

Table 3 BC/DR trends over time

		<i>Missing</i>	Overall	1988-1999	2000-2009	2010-2015	2016-2022	<i>P-Value</i>
n			53	3	16	15	19	
RT technique, n (%)	2D	<i>1</i>	4 (7.7)	2 (66.7)	2 (12.5)			<i>0.001</i>
	3D		26 (50.0)	1 (33.3)	11 (68.8)	9 (64.3)	5 (26.3)	
	IMRT		13 (25.0)			4 (28.6)	9 (47.4)	
	SBRT		6 (11.5)		2 (12.5)		4 (21.1)	
	Brachytherapy		3 (5.8)		1 (6.2)	1 (7.1)	1 (5.3)	
Credentialing procedure¹, n (%)	yes	<i>7</i>	31 (67.4)	1 (33.3)	8 (53.3)	9 (69.2)	13 (86.7)	<i>0.139</i>
	no		15 (32.6)	2 (66.7)	7 (46.7)	4 (30.8)	2 (13.3)	
Prospective², n (%)	yes	<i>5</i>	43 (89.6)	1 (33.3)	12 (80.0)	14 (100.0)	16 (100.0)	<i>0.002</i>
	no		5 (10.4)	2 (66.7)	3 (20.0)			
Number of cases, n (%)	1	<i>0</i>	33 (62.3)	3 (100.0)	6 (37.5)	12 (80.0)	12 (63.2)	<i>0.448</i>
	2		13 (24.5)		6 (37.5)	2 (13.3)	5 (26.3)	
	3		3 (5.7)		2 (12.5)		1 (5.3)	
	4		4 (7.5)		2 (12.5)	1 (6.7)	1 (5.3)	
Proportion of participating centers, median (%) [Q1,Q3]		<i>15</i>	90 [60,110]	40 [40,50]	80 [60,110]	90 [80,100]	100 [100,110]	<i>0.020</i>
Analysis expert, n (%)	Physicist and radiotherapist	<i>18</i>	10 (28.6)		1 (16.7)	4 (33.3)	5 (35.7)	<i>0.145</i>
	Radiation oncologist alone		9 (25.7)		1 (16.7)	4 (33.3)	4 (28.6)	
	None		1 (2.9)	1 (33.3)				
	Physicist alone		1 (2.9)				1 (7.1)	
	Other		14 (40.0)	2 (66.7)	4 (66.7)	4 (33.3)	4 (28.6)	
Objective tools³, n (%)	yes	<i>0</i>	29 (54.7)	1 (33.3)	8 (50.0)	8 (53.3)	12 (63.2)	<i>0.740</i>
	no		24 (45.3)	2 (66.7)	8 (50.0)	7 (46.7)	7 (36.8)	
Analysis of target volume delineation, n (%)	yes	<i>0</i>	42 (79.2)	2 (66.7)	12 (75.0)	14 (93.3)	14 (73.7)	<i>0.452</i>
	no		11 (20.8)	1 (33.3)	4 (25.0)	1 (6.7)	5 (26.3)	
Analysis of OAR delineation, n (%)	yes	<i>0</i>	33 (62.3)		10 (62.5)	12 (80.0)	11 (57.9)	<i>0.068</i>
	no		20 (37.7)	3 (100.0)	6 (37.5)	3 (20.0)	8 (42.1)	
Analysis of dosimetry, n (%)	yes	<i>0</i>	50 (94.3)	3 (100.0)	14 (87.5)	14 (93.3)	19 (100.0)	<i>0.432</i>
	no		3 (5.7)		2 (12.5)	1 (6.7)		

BC/DR : benchmark case/dummy run; OAR: organ at risk; IMRT: intensity modulated radiation therapy; RT: radiotherapy; SBRT: stereotactic body radiation therapy

Other : QA team or expert without precision, radiologist

1 : RTQA procedure required for centers to participate in the study and before the beginning of the study

2 : RTQA procedure performed before patients enrolment begins at each center, but not necessarily before the study begins overall.

3: Use of geometrical tool or index to assess delineation or dosimetry compliance

Table 4 ICR trends over time

		<i>Missing</i>	Overall	1988-1999	2000-2009	2010-2015	2016-2022	<i>P-Value</i>
n			60	8	16	18	18	
RT technique, n (%)	2D 3D IMRT SBRT Brachytherapy	<i>3</i>	15 (26.3) 25 (43.9) 10 (17.5) 3 (5.3) 4 (7.0)	5 (83.3) 1 (16.7)	7 (43.8) 6 (37.5) 1 (6.2)	3 (16.7) 9 (50.0) 4 (22.2) 1 (5.6)	3 (16.7) 9 (52.9) 5 (29.4) 2 (11.8) 1 (5.9)	<i>0.024</i>
Prospective ICR¹, n (%)	yes no	<i>3</i>	20 (35.1) 37 (64.9)	1 (12.5) 7 (87.5)	3 (20.0) 12 (80.0)	8 (44.4) 10 (55.6)	8 (50.0) 8 (50.0)	<i>0.136</i>
Proportion ICR vs enrolled patient², median (%) [Q1,Q3]		<i>10</i>	80 [30,100]	100 [90,100]	90 [30,100]	80 [70,100]	80 [10,100]	<i>0.761</i>
ICR planned in the protocol³, n (%)	1 2 3 5 6 All Other	<i>2</i>	6 (10.3) 1 (1.7) 3 (5.2) 5 (8.6) 1 (1.7) 37 (63.8) 3 (5.2)	1 (12.5)	3 (20.0) 1 (6.7)	1 (5.9) 1 (5.9) 1 (5.9)	5 (27.8) 1 (5.6) 1 (5.6) 9 (50.0) 2 (11.0)	<i>0.373</i>
Proportion of participating centers, median (%) [Q1,Q3]		<i>24</i>	100 [90,100]	100 [90,100]	100 [60,100]	100 [90,100]	100 [90,100]	<i>0.750</i>
Subjective analysis expert, n (%)	Radiation oncologist alone Physicist and radiation oncologists Physicist alone Other	<i>17</i>	16 (37.2) 10 (23.3) 1 (2.3) 16 (37.2)	2 (33.3) 1 (16.7)	4 (33.3) 3 (25.0) 5 (41.7)	7 (58.3) 1 (8.3) 4 (33.3)	3 (23.1) 5 (38.5) 1 (7.7) 4 (30.8)	<i>0.574</i>
Analysis of target volume delineation, n (%)	yes no	<i>1</i>	42 (71.2) 17 (28.8)	4 (57.1) 3 (42.9)	12 (75.0) 4 (25.0)	13 (72.2) 5 (27.8)	13 (72.2) 5 (27.8)	<i>0.848</i>
Analysis of OAR delineation, n (%)	yes no	<i>6</i>	20 (37.0) 34 (63.0)	7 (100.0)	2 (13.3) 13 (86.7)	10 (58.8) 7 (41.2)	8 (53.3) 7 (100.0)	<i>0.005</i>
Analysis of dosimetry, n (%)	yes no	<i>0</i>	55 (91.7) 5 (8.3)	7 (87.5) 1 (12.5)	13 (81.2) 3 (18.8)	18 (100.0)	17 (94.4) 1 (5.6)	<i>0.233</i>

ICR: individual case review; OAR: organ at risk; IMRT: intensity modulated radiation therapy; RT: radiotherapy; SBRT: stereotactic body radiation therapy

Other : QA team or expert without precision, radiologist

1 : ICR analyzed before patient treatment begins

2: Proportion of performed ICR based on the total number of included patient in each study

3: Number of ICR planned in trial protocol for each center (more frequently the first N included patients or N random patients)

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PERSPECTIVES

Le contrôle qualité de la radiothérapie dans les essais cliniques est une procédure importante pour garantir la qualité du traitement des patients inclus dans l'étude, ainsi que la fiabilité des résultats. Cependant, cette étude a mis en évidence le faible nombre d'essais cliniques réalisant un contrôle qualité, de l'ordre de 1,14% des études, et le nombre encore plus faible de ceux qui les publient. De manière surprenante, après la publication des résultats du TROG 02.02 et la création du GHG en 2010, alors qu'une augmentation des procédures de contrôle qualité aurait été attendue, aucune augmentation significative n'a été constatée avec une stagnation de la proportion des contrôles qualité prévus dans les protocoles d'étude d'environ 1 %.

Des techniques de radiothérapie de plus en plus avancées se développent régulièrement. Ceci est associé à des contrôles qualité qui s'avèrent être de plus en plus complexes et complets au fil du temps.

De nombreux types différents de contrôles qualité ont été retrouvés dans cette étude, sans harmonisation de leurs définitions ou caractéristiques de procédure. Ainsi nous avons retrouvé une part importante d'études réalisant une analyse uniquement visuelle par un ou plusieurs experts de la délinéation ou de la dosimétrie des plans. Certaines études ont effectué une analyse objective de ces paramètres mais utilisant des outils géométriques d'analyse multiples et dont la définition variait d'une étude à une autre. De la même manière, une majorité des études comparaient la délinéation des volumes cibles et organes à risque à un volume « contrôle » délinéé par un expert, le plus souvent l'investigateur principal de l'étude.

Il semble donc nécessaire d'harmoniser ces outils ainsi que le processus d'analyse de la délinéation et de la dosimétrie des plans de traitement. De futures études pourraient ainsi permettre de caractériser le type de contrôle qualité et les différents outils d'analyse et leurs choix afin de déterminer la procédure de contrôle qualité la plus adéquate et la plus fiable en fonction du type et de l'objectif de l'étude.

Enfin, il paraît également intéressant d'évaluer l'apport des nouvelles technologies, notamment de l'intelligence artificielle, dans la qualité des traitements ainsi que dans le contrôle qualité des plans de traitement pouvant possiblement permettre une meilleure fiabilité avec un gain de temps par rapport aux procédures classiques.

ANNEXE

Liste des abréviations

AI: artificial intelligence

BC/DR: benchmark case / dummy run

DL: deep learning

EORTC: European Organisation for Research and Treatment of Cancer (Organisation Européenne pour la Recherche et le Traitement du Cancer)

FQ: facility questionnaire

GHG: Global Clinical Trials RTQA Harmonization Group (groupe d'harmonisation global des essais cliniques)

GI: gastro-intestinal

HNSCC: head and neck squamous cell carcinoma

ICR: individual case review

IMRT: intensity modulated radiation therapy

ML: machine learning

NCI: National Cancer Institute (institut national du cancer)

OAR: organ at risk

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

RT: radiotherapy

RTQA: radiotherapy quality assurance

SBRT: stereotactic body radiotherapy

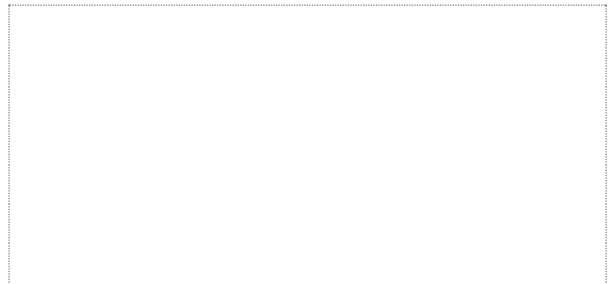
TROG: Trans Tasman Radiation Oncology Group

Vu, le Président du Jury,
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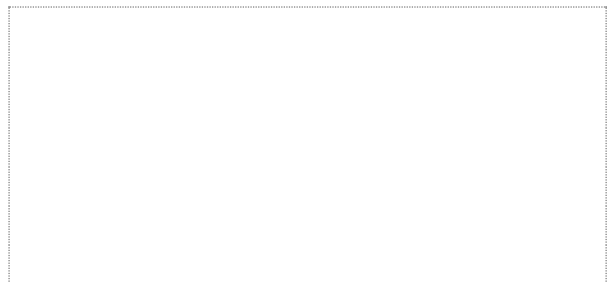
Professeur Juliette THARIAT

Vu, le Directeur de Thèse,
(tampon et signature)



Professeur Stéphane SUPIOT

Vu, le Doyen de la Faculté,



Professeur Pascale JOLLIET

Evolution au cours du temps des contrôles qualité des essais cliniques en radiothérapie, une revue systématique de la littérature

RESUME

Le contrôle qualité de la radiothérapie est un processus systématique visant à évaluer la conformité d'un plan de radiothérapie par rapport aux directives des protocoles d'essais cliniques et constitue une étape essentielle pour garantir la fiabilité des résultats de l'essai. Dans le passé, certaines études ont montré que les écarts par rapport au protocole affectaient de manière significative les résultats de l'essai clinique et diminuaient la survie globale. Le but de cette étude était d'évaluer l'évolution et les paramètres influençant le type des procédures de contrôle qualité dans le temps.

Les caractéristiques des essais cliniques et leur propension à réaliser des contrôles qualité ont été examinées au fil du temps.

Parmi les 663 articles trouvés sur PubMed, 130 études ont été sélectionnées comme ayant mené un contrôle qualité entre 1988 et 2022. Parmi ces études, 96 essais ont publié leur résultat. Au cours de la même période, par rapport aux essais enregistrés dans la base de données Clinicaltrial.gov, 1,15 % et 0,85 % des essais ont réalisé et publié un contrôle qualité respectivement, sans tendance significative au fil du temps. Il a été retrouvé que les contrôles qualité étaient plus complexes et complètes au fil de temps.

Ainsi, cette étude met en évidence le faible nombre d'essais réalisant un contrôle qualité et le nombre encore plus faible de ceux qui le publient. Aucune augmentation significative n'a été constatée au fil du temps, alors que les techniques de radiothérapie se développent régulièrement. Les types de contrôle qualité varient considérablement dans le temps et une analyse plus poussée devrait être réalisée pour évaluer la procédure plus adéquate et la plus fiable.

MOTS-CLES

Contrôle qualité de radiothérapie ; Individual Case review ; Dummy Run ; Benchmark Case