REVIEW ARTICLE

RADIOTHERAPY: BASIC CONCEPTS AND RECENT TECHNIQUES ADVANCES FOR THORACIC MALIGNANCIES

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Abstract

Radiation therapy (RT) is a clinical modality treatment that uses ionizing radiation in the approach of malignant tumors, (and occasionally benign diseases). Since its inception, the goal of RT has been to cure cancer without excessive side effects. The most important factors affecting the results of RT are the tumor histology, its location and regional extent, the anatomic area of involvement and the geometric accuracy with which a calculated radiation dose is delivered. Radiotherapy is one of the basic treatment modalities in thoracic malignancies and is used across all histology types and stages. Technical developments of radiotherapy have further strengthened and redefined its place in the management of lung cancer. High precision intensity-modulated radiation therapy, volumetric modulated arc therapy, and stereotactic body radiation therapy (SBRT), coupled with management of tumor motion and on-board imaging, increased efficacy and markedly decreased treatment-related toxicity. With this brief review, the authors pretend to present basic concepts and recent techniques advances in the use of radiation therapy for thoracic malignancies.

Keywords: *radiotherapy, lung cancer*

INTRODUCTION

Radiation therapy (RT) plays a fundamental role in the multidisciplinary treatment and management of thoracic neoplasms, and in particular, RT is the most used non-surgical treatment modalitymore often used for lung cancer, the most common type of thoracic malignancies. Due to the recent technological progress in modern RT techniques and new fractionation paradigms, an improved therapeutic ratio has led to better long-term disease control and reduced radiation-related side effects[1]. The main purpose of RT is to give the maximum dose possible to tumor lesions, either benign or malignant, and simultaneously, minimize the dose of radiation in adjacent normal tissues, called organs at risk (OAR). The limiting factor of this therapeutic modality is the adverse reactions that may arise when the tolerance dose of these tissues is exceeded. The maximum tolerated dose corresponds to the dose threshold at which the adverse effects of the treatment overlap the therapeutic effects. Therefore, all efforts must be made to deliver a higher dose to the tumor to obtain a greater likelihood of cure [1,2].

In conventional RT, the relative biologic effectiveness of radiation is influenced by radiobiological determinants, the so-called '5Rs': Repair, Repopulation, Redistribution, Reoxygenation, and Radiosensitivity[3]. A linear-quadratic model prevails to describe the radiation response of the tumor, in which the α/β ratio is used to characterize the sensitivity of a particular tissue type to fractionation. Fractionation serves to decrease acute, and especially late, toxicity to surrounding normal tissue exposed to RT.

Commonly, curative RT is delivered in daily doses of 1.8–2.2 Gy for 5–8 weeks, whereas hypofractionation is defined as a delivery of greater than 2.2 Gy per fraction. With sophisticated advances in RT technologies, delivering higher doses of RT per fraction [i.e. increased biologically effective dose (BED)] in a shorter timeframe appears a safe option. Indeed, increased BED could be achieved with larger fraction sizes relative to conventionally fractionated RT. While early radiobiological studies had found that the major mechanisms of action of radiation were related to DNA damage and subsequent cell death of dividing cells, novel insights on radiation effects have uncovered the immunomodulatory properties of ionizing radiation[3,4]. There is no doubt about the growing evolution in the approach to oncological disease in recent years, and Radiation Oncology is no exception. As a result of a better understanding of the mechanisms underlying tumor genesis and its biological behavior, associated with technological developments in this area, we can now integrate new therapeutic solutions to treat this disease. The evolution towards more localized and precise treatments allowed the use of radiotherapy to treat tumor lesions that were not previously considered for this therapeutic modality. Currently, we carry out treatments that would have been unthinkable until a few years ago. We managed to overcome classic limitations, namely re-irradiation and irradiation of lesions close to OAR, such as the spinal cord, heart, lungs, bronchi, esophagus, trachea, liver, and great vessels. Dose escalation is only possible with the use of more advanced technology than Three Dimensional (3D) Conformal Radiation Therapy (3D-CRT), namely Intensity-Modulated Radiation Therapy (IMRT) and Stereotactic Body Radiotherapy (SBRT), as described below[5,6].Updated guidelines have incorporated many of the incremental improvements in radiotherapy planning and delivery. There are now more standardized definitions of target volumes, improvements in radiotherapy plan quality (including daily on-table treatment plan revisions) and reductions in OAR, all of which have increased clinician confidence to deliver ablative doses of radiation. Changes in thoracic radiotherapy guidelines have partly been driven by results of studies showing improvements in population outcomes following the implementation of new radiotherapy techniques[4,6]. Recent prospective trials in early-stage lung cancer, locally advanced NSCLC and oligometastatic (lung) cancer have also contributed to a changing perception of the role of radiation in multidisciplinary care[1,2,5]. The planning process involves a complex chain of events and successful treatment is dependent on optimization of each part of the process (tumor definition, simulation, treatment planning, treatment delivery) can be strengthened and enhanced by improvements in imaging and technologies[1,6]. Fundamental to this process is the accurate definition of the target volume. The close proximity of lung cancers to critical organs such as the spinal cord or oesophagus often limits the dose that can be given to the tumor. Accurate assessment of tumor versus benign tissue is vital if doses are to be increased without increasing toxicity. Dose escalation is an area of considerable research in lung cancer as several studies have shown promising results in terms of local control[1].

PLANNING PREPARATION

Once a patient has been selected for radiotherapy a planning computed tomography (CT) scan is acquired with the patient immobilized in the position in which they will be treated. The data from this scan are then transferred to planning systems. The clinician defines the target volume and dose limiting normal tissues and subsequently the planning process is continued by a physicist[4]. Since Positron Emission Tomography (PET) was approved for clinical investigation of pulmonary nodules in 1998, there has been unprecedented growth and development in technology and clinical applications to benefit patient care. Multiple modalities have come together, including PET with CT and, more recently, PET with MRI to form hybrid PET/CT and PET/MRI to improve the accuracy of diagnosis, staging,planning, and therapy response assessment. When used correctly, PET/CT can have a great impact on the planning of radiation therapy because of its unique biologic target volumes when compared with other modalities. There are practical considerations to consider in implementing PET/CT in radiation therapy planning, such as the needs of the PET/CT center, the types of scans to offer, workflow considerations between the PET/CT center and the radiation therapy planning center, PET/CT center growth and demand on schedules, and the desired impact PET/CT will have on radiation treatment planning[7]. A linear accelerator radiotherapy system is represented in Figure 1.

VOLUME DEFINITION

The volumes used for 3D conformal radiotherapy for thoracic malignancies are defined by the International Commission on Radiation Units (ICRU) report 50 and the supplement ICRU 628,9. The gross tumor volume (GTV) is the gross palpable, visible or demonstrable extent of malignant disease. To ensure adequate coverage of subclinical or microscopic disease a 3D margin may be added to the GTV known as the clinical target volume (CTV). In turn a further margin is required to account for technique-dependent variations such as positional inaccuracy for the individual, internal organ movement (e.g. breathing), and parameters of the treatment machine that may result in inadequate dose coverage of the CTV. The addition of this margin produces the planning target volume (PTV). In lung cancer planning, a margin of 1–2 cm is added to the disease visible on CT scan to produce the PTV[1,8,9]. Figure 2 shows an example of a radiotherapy treatment planning.

INTENSITY-MODULATED RADIATION THERAPY (IMRT)

IMRT is a high-precision technique that allows selective irradiation of the tumor, providing a higher gradient difference between the dose to the tumor volume and the

surrounding tissues, when compared to 3D-CRT. In 3D-CRT, the radiation fields are fixed, and the shape of the beams is molded to the target volume, administered with uniform intensity. In IMRT, the intensity of the treatment beam varies, making it possible to obtain a higher dose gradient. The radiation beams of the treatment field are modulated to irradiate the tumor according to its shape, avoiding exceeding the dose limits of organs at risk. For this purpose, the linear accelerator incorporates a dynamic multi-leaf collimator, which opens and closes individual leaves to shape the radiation beams, according to the required intensity. This allows the administration of an increased number of beams, at multiple angles and different planes. This approach is particularly useful when the tumor volume totally or partially encompasses a critical anatomical structure that has low dose tolerance, such as the spinal cord[10,11]. The main advantages of this technique are to increase local tumor control and survival, as well as decrease the acute and late side effects of radiotherapy, thus increasing the therapeutic gain. Since tumors have different shapes and sizes and are surrounded by healthy tissues, IMRT allows the safe delivery of a higher dose directed to the tumor, increasing the chance of tumor control[1,9,12,13].

The technique Volumetric-Modulated Arc Therapy (VMAT/RAPIDARC®) consists of the administration of radiation beams by a 360º rotation of the linear accelerator gantry around the patient. The field opening shape, the irradiation speed, and the dose rate are independently controlled, allowing for improvement in the conformity of the dose to the target volume, which drastically reduces the treatment time. This technique has enabled the treatment of some tumors which were previously impossible to treat, due to the proximity of normal dose-limiting structures[14–16]. The multi-institutional randomized clinical trial RTOG 0617 aimed to evaluate the impact of IMRT in the treatment of locally advanced lung tumors. IMRT showed better coverage of the PTV when compared to the 3D-CRT technique. Also, it allowed for a significant reduction in grade 3 pneumonitis, as well as in cardiac dose, reflecting an increased overall survival in the multivariate analysis[17].Thus, IMRT is associated with an improvement in quality of life, and its use is now routinely advocated[12].

STEREOTACTIC BODY RADIOTHERAPY (SBRT)

SBRT also has the objective of increasing the dose delivered to the tumor while limiting the dose on adjacent normal structures, which can be critical. It was defined by the American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO), as the administration of a dose per fraction > 6Gy, usually delivered in 1 to 5 treatment sessions. This approach, also known as "ablative radiotherapy" has unique radiobiological characteristics which enable an intense tumor response[18–21].

Some requirements for SBRT include:

- the precise location of the target lesion;

- the precise location of adjacent normal, dose-limiting organs;

- take into account internal movements such as breathing or swallowing, for instance.

- image guidance during the radiotherapy session, to verify the location of the target volume and be able to make adjustments to the position, if necessary.The tumor target volume is treated with millimeter precision. Thus, it is possible to obtain a dose escalation, by administration of a smaller number of sessions (in general, from 1 to 6 fractions), minimizing doses in adjacent tissues, with a consequent decrease of acute and late side effects. It is indicated for small, well-defined tumors with curative intent, for example initial-stage lung cancer, and in a palliative setting, namely in cases of cranial, bone, and lymph node metastases[5,18,19]. For locally advanced tumors, researchers from the University of Kentucky developed a prospective trial to evaluate the effect of an additional boost to the primary tumor, delivered with SBRT, after conventional treatment, to obtain a dose escalation at the level of residual injury. In this study, patients with stage IIIA and IIIB were treated with an average dose of 59.4 Gy, having posteriorly been submitted to a fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan, 1 month after the end of the treatment. The additional dose with SBRT was proposed if the residual disease was ≤5cm. The SBRT scheme was 6.5 Gy in 3 fractions for central tumors and 10 Gy in 2 fractions for peripheral tumors. The primary endpoint was to determine grade ≥3 pneumonitis, according to RTOG criteria. Despite dose escalation, authors didn't observe increased acute or delayed side effects. Studies by Higgins et al and Hepel et al have shown similar results. These studies, along with RTOG 0813, have proved that a rigorous delimitation of organs at risk, as well as contemplation of the dose limit constraints, are fundamental features when performing dose escalation, with the objective of better tumor control and protection of critical structures[19,22–24].

ROBOTIC RADIOSURGERY - CYBERKNIFE®

In the context of stereotactic radiosurgery, we must address robotic radiosurgery – Cyberknife®, a linear accelerator incorporated in a robotic arm, with differentiating versatility that allows the delivery of ablative doses to the tumor, with submillimeter precision, while minimizing toxicity to adjacent normal tissues (Figure 3 and 4). This aspect is crucial for obtaining an adequate tumor response with a higher quality of life[1,9,25]. It contemplates software that offers accurate and real-time information, by monitoring and correcting the robotic arm's position, according to the target's location through a three-dimensional tracking system that coordinates tumor positions with breathing cycles, without causing discomfort to the patient[26].

This technology has offered new opportunities in the treatment of lung cancer, namely:

- in early stages (I-II) considered inoperable, with medical contraindications for surgery, or in case of refusal by the patient;

- in centrally located tumors, due to proximity to critical organs such as the heart, esophagus, trachea, and bronchial tree;

- in re-irradiation setting (re-treatment in previously irradiated patients);

- in metastatic disease.

Better tumour targeting can improve tumour control rates, and different approaches have been endorsed in clinical practice guidelines. A recommended strategy for lung tumours involves the use of a 4-dimensional (4D) CT scan for treatment planning, and all observed motion is used to generate a so-called internal target volume (ITV). However, in cases where tumours exhibit significant motion, the ITV approach can expose the healthy lung to a higher radiation dose. Daily pre-treatment verification of the tumour position is mandatory, and this is commonly performed using integrated cone-beam CT technology on a conventional linear accelerator. However, as tumour motion during treatment delivery can exceed that observed on pre-treatment 4D-CT imaging, motion monitoring during radiation delivery is desirable. Respiration-gated radiotherapy refers to radiation delivery that is restricted to a predefined tumour position and/or phase of the patient's respiratory cycle. Another approach in clinical use is tumour tracking, where the treatment beam continuously follows or is shaped to the tumour position. Such so-called active motion management approaches can permit use of smaller treatment volumes. However, motion management involving implantation of fiducial markers carries risks, especially in the elderly and frail patients. Noninvasive monitoring of respiratory movements is possible using spirometric devices or infrared or optical cameras to monitor surface breathing motion, although these approaches can fail to accurately capture variations in tumour position[4–9]. Recent advances in radiotherapy technology aim to circumvent the need for implanted fiducials, or other surrogate markers, to capture tumour motion in real-time. Since 2014, direct tumourvisualisation during radiation delivery has become possible with use of so-called magnetic resonance-guided radiotherapy devices. These hybrid machines incorporate both magnetic resonance imaging and radiotherapy technology into a single treatment system, which allows for continuous acquisition of magnetic resonance images during treatment. On-board magnetic resonance technology facilitates tumour gating without additional radiation exposure, and enables daily on-table plan adaptation, which improves treatment plans if doses to the tumour and/or critical organs are suboptimal due to changing anatomy. Magnetic resonance-guided lung SABR can be delivered with high precision, to significantly smaller target volumes than with a traditional motion-encompassing ITV approach. In addition, the safety of SABR delivered to tumours in the proximity of critical organs at risk is improved using magnetic resonance guidance[1,27,28].

RESPIRATORY GATING FOR RADIOTHERAPY

Taking into account the respiratory movements has always been a major concern of thoracic radiotherapy. The development of conformal radiotherapy using reduced radiation fields, with or without intensity modulation, and above all the growing interest for hypofractionated stereotactic body radiotherapy, further enhanced this concern. In 1987, an American team noticed that treatment in deep inspiration spared parts of the lungs, and they suggested a need to develop "Radiotherapy Gated to Respiration". The term "gating" was subsequently used to designate a variety of different practices. Five main strategies are currently used to reduce respiratory motion effects: integration of respiratory movements into treatment planning (geometrical or dosimetric), forced shallow breathing with abdominal compression, breath-hold techniques (active or voluntary), respiratory gating techniques, and tracking techniques[4–9,12,18,19,29].Traditionally, according to International Commission on Radiation Units and Measurements (ICRU) recommendations, tumor motion is taken into account by adding a specific security margin (internal margin) around the clinical target volume (CTV), in order to create the internal target volume (ITV). Positioning uncertainties are then added to create the planning target volume (PTV)[29]. The integration of respiratory movements into treatment planning improves the quality of computed tomography (CT) images and therefore the accuracy of contouring. It is now accepted that the apparent position of intrathoracic organs obtained by a free-breathing CT scan is not representative of an average position between inhalation and exhalation. The use of respiratory gating during the CT simulation session allows the acquisition of the anatomical data and then the irradiation of the target volume in a specific respiratory phase. As technology advances, technological developments in radiotherapy for lung cancer, including respiratory-gated radiotherapy, should allow dose escalation while maintaining a similar complication rates. As a result, it could improve local control or even overall survival[30].

RADIOSURGERY FOR OLIGOMETASTATIC DISEASE

Radiosurgery is increasingly used for the treatment of patients presenting with up to five metastases, or so-called oligometastatic disease. In patients with limited metastatic lung cancer who do not progress after first-line systemic therapy, local consolidative therapy can improve progression free survival compared to standard treatment. The randomised SABR-COMET trial demonstrated that radiosurgery delivered to one to five metastatic lesions can improve long-term survival compared to standard of care in a mixed cohort of patients presenting with different primary tumours. Nearly half of all metastases treated in the SABR-COMET trial were located in the lung, and lung radiosurgery accounted for two of three fatal toxicities observed in the trial. Additional drivers

Figure 1

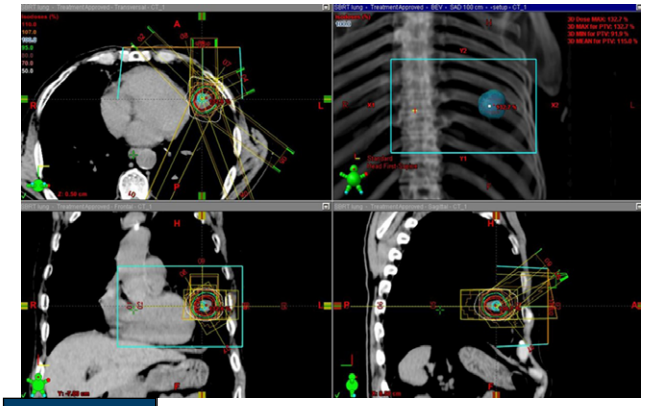

Figure 2

of the need for improving SABR delivery are the suboptimal local control rates observed for some patients, with an overall long-term local control rate of only 63% for metastases in the SABR-COMET trial[31–33]. Radiosurgery has also been used for the treatment of isolated thoracic nodal recurrences. The results of ongoing trials, such as SABR-COMET-10, may lead to a broadening of the indication for patients to undergo radiosurgery for multiple lesions. Improved radiosurgery delivery techniques will be required in such patients in order to reduce lung doses. Scheduling radiosurgery treatments to multiple sites between cycles of systemic therapy will be challenging, and this may be facilitated by delivering shorter treatments. The safety, efficacy and cost-effectiveness of single-fraction radiosurgery for oligometastatic patients with one to three lung metastases are being compared to a four-fraction radiosurgery regimen in a randomised phase II trial, which has completed accrual[31,32,34].

PALLIATIVE RADIOTHERAPY FOR LUNG CANCER

It may be given to improve breathlessness, chest pain, cough and pain caused by metastases. It also has an important role in the management of brain metastases, in an obstruction caused by a superior vena cava syndrome and in cases of spinal cord compression[35,36].

TOXICITY OF RADIOTHERAPY AND ITS ASSOCIATION WITH CONCOMITANT THERAPIES

Similar to other therapeutic modalities, Radiotherapy can cause some side effects, which can vary according to the patient. It is necessary to take into account the type and location of the tumor, the treatment technique, the general condition of the patient, and its collaboration in following the recommended medical indications, to minimize the referred side effects inherent to the treatment choice37. It should be noted that some factors may already be present before the start of treatment, such as pulmonary fibrosis, which may strongly condition tolerance to treatment38,39. The most notorious side effects, which can be aggravated by the use of systemic therapy, whether concomitant or sequential, are:

- fatigue, which can become disabling for daily activities and can last for about 2 months after the end of treatment;
- cough, dyspnoea, and chest pain;
- skin changes that may include erythema, edema, dry desquamation and itching;
- anorexia and esophagitis, which tend to resolve, in most cases, within 2 to 3 weeks after the end of treatment;
- radiation pneumonitis, which can appear 3 to 6 months after the end of radiotherapy, and may present with dry cough and dyspnea, sometimes necessitating the institution of corticosteroid therapy and/or oxygen therapy[40,41–43].

HOW TO PREVENT AND TREAT COMPLICATIONS

Radiotherapy side effects are more severe when:

- the target volumes are large, namely greater than 5cm;
- there is close or even direct contact with dose-limiting structures;
- we use higher doses per fraction;
- radiotherapy treatment is carried out with systemic, concomitant, or sequential therapy.

Immediate side effects may appear 6 to 12 hours after treatment. These are occasional and include nausea, vomiting, and chest discomfort, particularly when using higher doses per fraction (generally ≥ 6 Gy). The drugs most used in the management of these symptoms are Paracetamol, Metoclopramide and Dexamethasone (4mg every 12 hours, for one day). Acute side effects generally appear 2 to 4 weeks after the end of treatments. Esophagitis is usually treated

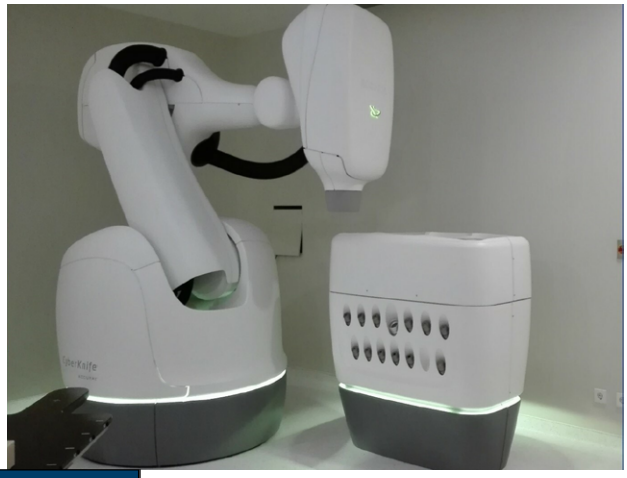

Figure 3

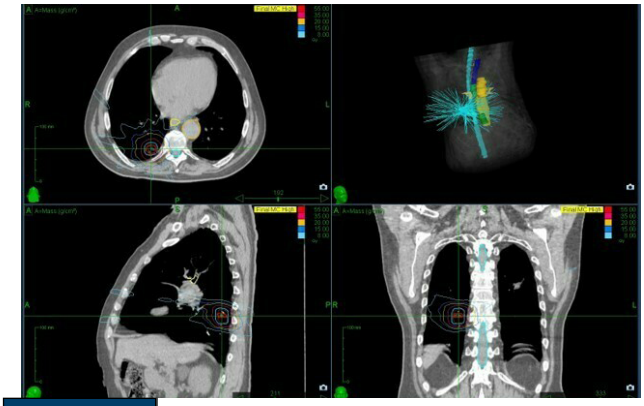

Figure 4

with Sucralfate, and analgesia such as soluble Paracetamol may be required[44,45]. We cannot rule out the possibility of esophageal candidiasis, treatable with Fluconazole 50mg per day, for 7 days[45]. Late side effects typically appear 6 weeks after the end of treatments and can last beyond 12 weeks. The most frequent late secondary effect is radiation pneumonitis, which can lead to usually a dry cough and dyspnea. It must be treated with corticosteroids for a period of 4 to 6 weeks, depending on the severity of the symptoms. Initially, Prednisolone 20mg/day is used during the first 2 weeks, followed by dose reduction, which should be gradual until the 6th week. The use of corticosteroid therapy in patients with radiogenic pneumonitis also helps to prevent late pulmonary fibrosis[46–48]. Cutaneous side effects can arise when the lesions are located peripherally and/or when high doses of radiation reach the skin. These usually include grade 1 erythema, dry skin, and itching, wherein the application of trolamine and moisturizing cream is usually sufficient[49,50].

CONCLUSIONS

Radiotherapy is an important modality used for the treatment of lung cancer. Seventy-seven percent of all patients with lung cancer have an evidence-based indication for radiotherapy, although it is often underutilized. Radiotherapy can be used as curative or palliative treatment across all stages of disease. Technological advances have allowed better radiotherapy targeting of tumours and reduced incidental irradiation of surrounding normal tissues. This has expanded the indications for radiotherapy in lung cancer and improved outcomes both in terms of increasing survival and reducing toxicity. It is important to examine the current role of radiotherapy in lung cancer, discusses the evidence behind this and identifies future directions in the radiotherapy treatment of lung.

Recent advances in radiation therapy have contributed to the improvements observed in the survival of patients presenting with a lung cancer. Clear examples of this are the decreasing rates of non-treatment in early-stage lung cancer in population studies and the survival gains observed in trials incorporating immunotherapy following radiation therapy in locally advanced tumors. In many parts of the world, the lack of patient access to these newer techniques remains an impediment. Similarly, as treatment options become more complex, such as for oligometastatic lung cancer, the role of the multidisciplinary tumour board in selecting appropriate strategies will be paramount.

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