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Perspectives and Commentaries

Radiotherapy in Non-small Cell Lung Cancer: Present Progress and Future Perspectives

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IN MOST Western countries lung cancer is the number one cancer killer and its incidence is still rising, particularly in women [1]. One of the major considerations in the treatment of lung cancer is that the majority of patients present with unresectable lesions at the time of diagnosis. For many years, radiotherapy has played an important role in the management of patients with lung cancer. Radiation has been used as a curative modality, but most often as a palliative treatment for distressing symptoms produced by either the intrathoracic tumor and/or its metastatic spread. During the past decade, a better knowledge of the natural history of lung cancer, coupled with extraordinary technological advancements and improved cooperation with other disciplines, has led to a better understanding of the role played by radiotherapy in the management of this disease.

This review will focus mainly on radiation treatment of the non-small cell lung cancer (NSCL): squamous cell, large cell and adenocarcinomas.

At diagnosis at least one-third of all patients with lung cancer are found to have unresectable disease. In these patients radiation has been used for several decades as the primary therapeutic modality, but its exact role has not yet been well defined. Although it has been firmly established that a few patients can be cured with radiation therapy (5-yr survival $\leq$10% in most series), there are still two different opinions as to its actual purpose: an immediately curative or a more conservative approach (Table 1) [2–7]. Some investigators advocate an immediate and aggressive radiation therapy treatment using doses above 50 Gy, which appear to be necessary to achieve local control of the disease and thus cure [2, 8–12]. Others advocate a more conservative approach, waiting to treat patients when symptoms develop and then using only moderate doses of radiation [5, 13]. The latter attitude is based on observations indicating that survival after irradiation, even with a curative intent, is poor because of a high incidence of distant metastases. This conclusion tends to be supported by a few reported randomized trials. Morrison compared surgery to radiation therapy with 45 Gy given in 4 weeks for squamous cell carcinoma; at 4 yr survival rates were 30% with surgery and only 6% for the irradiated group [14]. In 1968 Roswitt *et al.* reported a 22% 1-yr survival after 40–50 Gy given in 4–5 weeks, in contrast to 16% for controls [15]. The Oxford group compared no treatment until symptoms occurred, immediate radiotherapy (40 Gy delivered in 4 weeks with orthovoltage), chemotherapy or a combination of these two modalities; the mean survival time was similar for all the different treatments employed [13]. However, the following comments are in order: patients had inoperable (large) tumors, no systematic staging system was used and the radiation dose offered was certainly too low to achieve any adequate tumor control.

Different modern diagnostic procedures, which include gallium scans, bone and liver scintigrams, echography and computed tomography (CT), allow for more precise and accurate staging of lung tumors. Therefore patients with metastatic disease could be excluded from an aggressive (curative) radiation approach. Furthermore, a conservative approach, waiting for the disease to become symptomatic, implies that achieving local tumor control with radiation would not

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Table 1. Survival rates after radiotherapy for patients with inoperable lung cancer

Ref.	Patient No.	Survival rate (%) at: 1 yr	3 yr	5 yr	Comments
[3]	284	30	-	6	no selection
[5]	513	36	-	6	
[6]	348	-	9	5.6	
[2]	104	50	19	16	favorable group
	99	31	0	-	unfavorable group
[4]	96	65	22	12	squamous cell ca.*
[7]	40	75	27	225	operable non-sccl

*ca. = carcinoma; sccl = small cell carcinoma of the lung.

influence survival. On the contrary, during the last few years several studies have shown that control of the primary lung tumor is associated with a significant prolongation of survival and appears to be a requirement for cure. For example, in a series of 72 patients with unresectable squamous cell carcinoma of the lung treated with a dose higher than 50 Gy, Coy *et al.* reported a 2-yr survival rate of 69% for complete responders, 26% for partial responders and 11% for non-responders [4]. Similar results have been reported by several other groups (Table 2) [8, 9, 11, 12, 16–18].

Table 2. Relationship between tumor response and survival in non-small cell lung cancer

Ref.	Response	Patient No.	Survival: Median (weeks)	1 yr (%)	3 yr (%)
[4]	CR*	35	-	83	54
	PR	19	-	84	5
	NR	18	-	50	6
[13]	PR	57	58	57	-
	NR	75	28	37	-
[18]	CR	14	63.7	± 75	-
(VALG)	PR	116	46.7	± 45	-
	NR	213	31.0	± 30	-
[11]	CR	63	68.8	-	-
(RTOG)	PR	144	44.4	-	-
	NR	168	30.6	-	-

*CR = complete response; PR = partial response; NR = no response.

Therefore, from the radiation oncologist's point of view, all efforts should be made towards a better loco-regional control; this should be more efficient when the least bulk of tumor is present; thus, waiting may limit the effectiveness of irradiation.

RADIATION PARAMETERS

Optimal dose

The optimal dose of radiation is still subject to debate. In the past, many studies used only survival as an endpoint without looking at the loco-regional tumor control or to prognostic factors such as stage, grade, performance status or weight loss. Information is now available from different sources which include data from autopsies, surgical specimens or randomized clinical trials.

Several clinical studies have shown an increase in tumor response, loco-regional control and even survival with doses in excess of 50 Gy [8–10, 12, 17]. In a series of 67 autopsies, Rissanen *et al.* reported no residual tumor in the irradiated volume in 18 cases; all of them received more than 40 Gy and the tumor was always smaller than 8 cm [19]. When surgical specimens were analyzed after planned preoperative irradiation, the tumor was sterilized in 27–35% of the cases treated with doses of 40–55 Gy [20, 21]. In all these studies the effect of radiation dose was assessed retrospectively and selection of patients may have influenced these results. However, the RTOG carried out a prospective randomized trial looking for the best dose–time schedule in NSCL cancer [11]. Four regimens were compared: three continuous radiation schedules with a daily dose of 2 Gy to a total of 40, 50 and 60 Gy and a split-course schedule (5 × 4 Gy in 1 week followed by 2 weeks of rest and another series of 5 × 4 Gy for a total of 40 Gy). The lowest doses (40 Gy) given either continuously or with the split-course technique were clearly inferior to 50 or 60 Gy both in terms of response rates and loco-regional control: intrathoracic relapse rates were 52% with 40 Gy, 41% with 50 Gy and 30% with 60 Gy. Nevertheless, there were no statistically significant differences in the 2-yr survival: 19% with doses of 50 Gy or more and 11% with doses of 40 Gy. An interesting observation was the relation between tumor size, dose, tumor response and local control: for tumors smaller than 6 cm, local relapses were significantly lower for doses of 50 Gy or more; in contrast, there were no differences for tumor greater than 6 cm or non-measurable lesions. All these findings indicate that the optimal dose of radiation for lung cancer must be in the range of 50–60 Gy.

Treatment quality

Other characteristics of the treatment are also important factors not only for tumor control, but also for the unavoidable radiation damage induced to the normal tissues. In lung cancer the treated volume must include the tumor with a safety margin, the ipsilateral and contralateral hila, the mediastinum and possibly both supraclavicular areas. Inadequate coverage seems to have a detrimental effect on survival: in the RTOG study median survival dropped from 46 to 20–30 weeks [11].

Thoracic irradiation with high doses represents a challenge to radiation oncologists related to the limited tolerance of vital organs within the irradiated field: spinal cord, lungs and heart. All radiation-induced damage is time–dose–volume-related [16, 22–24]. The threshold dose for radiation myelitis with conventional fractionation is 45 Gy and there is an increased risk for larger fractions given over a shorter period of time. Radiation pneumonitis and fibrosis are directly related to the dose and inversely related to the volume treated: doses in excess of 25 Gy delivered to the whole lung may produce permanent damage.

Nevertheless, recent technical developments have helped to improve the quality of the radiation treatment: CT, computed treatment planning, sharper radiation beams and individually tailored fields of irradiation to cover precisely the tumoral extent. CT has brought two major advances: it provides precise information about tumoral extension and its relationship to surrounding structures and/or dose-limiting organs and it offers cross-sectional data throughout the proposed treatment volume, giving quantitative information for tissue inhomogeneity corrections. The information provided by CT has been shown to change the treated volume in one-third of patients with lung cancer [25]. Precise treatment with oblique ports, shrinking fields following suitable responses and also careful shielding allow delivery of doses in excess of 50 Gy without a major increase in radiation toxicity [8, 9].

Unconventional fractionation

Split-course schedule. During the last decade unconventional fractionation schedules (split-course, hypofractionation, hyperfractionation...) have stimulated new interest. The split-course technique, using daily fractions for 1–2 weeks followed by a rest period of 2–4 weeks and a second course of daily irradiation, has become popular. This technique was already advocated by Scanlon in 1959 [26] and by Sambrook in 1964 [27]. Both investigators observed a better treatment tolerance. Theoretically, the rest period allows for a reparative process of the radiation damage, which is more rapid in normal tissue than in tumors. It also allows for a better reoxygenation of hypoxic cells as the tumor is reduced in size; this should make the remaining, better oxygenated tumor more sensitive to a second course of irradiation. Besides these theoretical reasons, the main advantage of split-course schedules is certainly that of an improved convenience to patients and physicians: there is a reduction in the number of treatments given, a rest period, and also it allows physicians more prolonged periods of observation, which can avoid the delivery of the second course of irradiation in the presence of progression.

Several studies have been conducted to assess the effectiveness of split-course schedules compared to the more conventional daily treatments [11, 28–34]. In the already mentioned RTOG study the split-course schedule (5 × 40 Gy in 1 week repeated after 3 weeks of rest) yielded lower 1- and 2-yr survival rates, lower response rates and poorer local control than continuous irradiation with 50 or 60 Gy [11]. These findings do not confirm the initial report of Abramson and Cavanaugh showing a benefit with this type of split-course schedule; however, in that study the 1-yr survival was actually very poor in the control group (14%) [28]. Other trials have shown no differences between the two techniques of irradiation either in terms of survival or response rates (Table 3) [30–33]. The only conclusions that can be drawn is that split-course schedules are certainly no more efficient or toxic than continuous irradiation provided that adequate doses and proper protection are given. Furthermore, the negative findings of the RTOG studies do not constitute proof that the split-course approach, in general, may not be valid; there are many different types of split-course schedules which can deliver very different biological doses. The split-course radiation technique certainly remains a more convenient schedule for a combined approach with cytotoxic drugs. However, there are some specific problems with the use of split-course schedules and their large daily fractions: the incidence of late effects, particularly radiation myelitis, is increased [35].

Hypofractionation. Schedules using large fractions of 4–6 Gy given in a particular continuous or interrupted fashion were often used for technical conveniences: hyperbaric oxygen treatment, overloaded treatment units, patients living at long distances from a radiation center. This approach has gained a new interest with the advent of radiosensitizers, radioprotectors and the use of integrated chemotherapy programs.

For lung cancer, once-a-week radiation has

Table 3. Split-course vs conventional radiation: randomized trials

Ref.	Histology	Treatment	Patient No.	Survival (%) 1 yr	2 yr	3 yr	Response rate (%)	Local relapse (%)
[32]	ALL	50 Gy 5 weeks	158	27	-	7	56	-
		27.5 Gy 2.5 weeks → 27.5 Gy 2-5 weeks	105	29	-	7	70	-
[30]	sq.c.ca.*	50 Gy 5 weeks	25	36	-	4	-	-
		25 Gy 2 weeks → 25 Gy 2 weeks	37	32	-	8	-	-
[28]	ALL	60 Gy 6 weeks	42	14	-	-	-	-
		20 Gy 1 week → 20 Gy 1 week	42	43	-	-	-	-
[11]	sq.c.ca.	20 Gy 1 week → 20 Gy 1 week	161	-	11	-	46	51
		40 Gy 4 weeks		-		-	51	
	adenoc.	50 Gy 5 weeks	76	-	19	-	66	42
	nscl	60 Gy 6 weeks	64	-		-	61	35
[31]	ALL	20 Gy 1 week → 20 Gy 1 week	51	12	-	-	-	-
		30 Gy → 30 Gy	46	26	-	-	-	-
[33]	sq.c.ca.	20 Gy 1 week → 20 Gy 1 week	137	-	9	-	36	no dif.
		30 Gy 3 weeks → 30 Gy 3 weeks	132	-	11	-	32	41
[29]	ALL	60 Gy 6 weeks	56	36	-	-	58	-
		20 Gy 2 weeks → 20 Gy 2 weeks → 20 Gy 2 weeks	38	38	-	-	63	-

*sq.c.ca. = squamous cell carcinoma; adenoc. = adenocarcinoma; nscl = non-small cell carcinoma.

been mainly used by Schumaker: patients were treated with one large single fraction of 5 Gy delivered weekly over 12 weeks to a total of 60 Gy. Survival was similar to that obtained with more conventional schedules [36]. In a pilot study conducted in Rochester this program yielded a high response rate (75%), a lower loco-regional failure rate and, most importantly, it was very well tolerated by the patients; the radiation-induced esophagitis was not seen during the course of the treatment. The number and severity of radiation-induced fibrosis was not increased and radiation myelitis was not observed. Nevertheless, the radiation fields were usually reduced after 30 Gy to boost only the primary target with concomitant spinal cord protection [37].

The major concerns with a hypofractionated treatment regimen are the potential risk of increased late toxicity and also a possible reduction in tumoral control. Using histologic examinations of bronchial tumors removed at operation or autopsy following radiation, Eichorn observed a higher proportion of negative specimens after a low daily dose when this was compared to large fractions: 53 vs 13% for operable tumors and 29 vs 18% for inoperable tumors [38]. In a review of the experience at the Medical College of Wisconsin, the reduction in the number of fractions per week was associated with a decrease in tumor control [39]. Prospective randomized trials are presently on-going to assess the effectiveness and late damage occurring with a hypofractionated schedule. Preliminary results show a better short-term survival for patients treated with 51 Gy given in 17 fractions of 3 Gy once weekly when compared to a continuous irradiation of 50 Gy in 5 weeks: the mean survival was respectively 11.5 vs 8 months [40]. At the University of Maryland preliminary reports of a randomized trial comparing conventional daily 2 Gy for 60 Gy in 6 weeks to 5 Gy once-weekly for 60 Gy in 12 weeks indicates a better tolerance, a higher response rate and no differences in late effect or survival with the use of the hypofractionated regimen [41].

RADIATION INNOVATIONS

Even with the best radiation schedule, loco-regional relapses and distant metastases remain as major issues against success. There are several approaches to improve radiation therapy effectiveness: increasing the biological dose to the tumoral tissues, increasing the tumor's sensitivity to radiation (radiosensitization), increasing normal tissue threshold for radiation damage (radioprotection) or adding a systemic treatment to try to control distant metastases.

Human tumors are composed of both oxic and hypoxic cells. The former are located at the periphery of tumors and are very sensitive to fractionated irradiation whereas hypoxic cells are more centrally located and radioresistant. Oxygen concentration at the tumoral level is a critical factor to enhance and permit the full effect of

radiation. Using multiple fractions of radiation, reoxygenation occurs: cells that were relatively hypoxic during exposure to a previous dose may become better oxygenated and therefore more sensitive at the time of subsequent doses [42]. Different approaches have been developed to overcome these problems and they will be discussed briefly.

Hyperbaric oxygen

This is one possibility to increase the oxygen content and effectiveness of irradiation. As oxygen is transported by hemoglobin in the blood its concentration can influence the control of the tumor by radiation. Uterine cancer victims with hemoglobin levels below 12 mg% had a significantly lower pelvic control (regardless of the stage of the disease), which increased after a transfusion done prior to irradiation [43]. In clinical practice the use of hyperbaric oxygen requires a complicated and expensive set-up. This technique was mainly studied by the Medical Research Council in the U.K. and showed some improvement in local control with advanced cancer of the cervix [44]. In Portsmouth the schedule of irradiation was the most important factor in defining the role of hyperbaric oxygen in lung cancer: when small daily conventional fractions were used there were no differences in survival, but when six fractions of 6 Gy were given in 18 days, survival at 2 yr for squamous cell carcinoma was 24.6% with hyperbaric oxygen and only 12.4% for irradiation in air [45]. In another randomized trial patients were treated with 12 × 4 Gy in air or hyperbaric oxygen; local control and survival were similar in both arms [46]. Nevertheless, this treatment is still limited by technical difficulties.

Radiosensitizer

Another approach to overcome the problem of hypoxia relates to drugs which could selectively increase the sensitivity of hypoxic cells and which would be easier to use than the hyperbaric oxygen chamber. Following the work of Adams *et al.*, several compounds (nitroimidazoles) have been identified which seem to increase, both *in vitro* and in experimental tumors *in vivo*, the sensitivity of hypoxic cells provided that an adequate concentration of the compounds reach the tumors [47, 48]. However, the full exploitation of available radiosensitizers is limited by toxicity: peripheral and central neuropathies are observed with total doses higher than 10 g/m^2 in 1 week or 15 g/m^2 in 6 weeks. This toxicity has curtailed the use of these compounds and has imposed specific new strategies to accommodate them: larger and fewer fractions of radiation to use the maximum benefit of each drug dose and still avoid exceeding the toxic dose level; high doses of the drug given with a few conventional fractions or multiple daily fractionation schedules; and finally low doses of the drug given with a conventional treatment [49].

Several phase III studies with radiosensitizers are on-going in many different tumors; most of them have not shown any improvement with the use of these substances for lung cancer. Two clinical trials have been published: patients with limited disease were treated with 35 Gy in 6 fractions over 3 weeks or with a split-course schedule (5 × 40 Gy repeated after 3 weeks); in both studies misonidazole did not improve the local control of the survival [50, 51]. New and potentially better radiosensitizers are being developed; a less toxic drug is needed which would be more easy to use with a daily conventional fractionation program.

Hyperthermia and high linear energy transfer (LET) radiation

Two other approaches are still under investigation for lung cancer: hyperthermia and high LET radiation. For the former the major problem lies in technical limitations to produce and measure controlled hyperthermia for deep-seated structures [52]. High LET radiations differ from photon radiations in that they are less dependent on oxygen concentration and replication cell-cycle kinetics, and because they can produce more damage at the cellular level by a much denser ionization. The particle beams most commonly used are fast neutrons; theoretically, they can be of some benefit in the treatment of lung cancer. However, the present available data on a limited number of patients do not show any major differences with photon beam treatments [53]. Laboratory and clinical pilot studies have indicated that combining fast neutrons with conventional photon irradiation (mixed beam) may achieve an enhanced therapeutic ratio when compared with fast neutrons alone. An RTOG study is on-going to test this hypothesis in lung cancer. Nevertheless, investigations of fast neutrons must still concentrate on trying to improve the quality of the equipment, particularly when neutrons are generated from high-energy cyclotrons which will require better shaped fields, and also to identify the tumors that will be more suitable for this treatment.

Systemic treatment

Combined modality. Distant metastases are the most common pattern of failure in lung cancer; a systemic type of treatment is by necessity in order [10, 17]. Chemotherapy has been used for many years in non-small cell cancer, but most studies

have not shown improvement [54]. Some new drug combinations, particularly with cisplatin, appear to achieve better results [55–57]. Therefore it would be interesting to test them in combination with loco-regional irradiation. However, the optimal timing of drug and radiation has certainly not been defined. Chemotherapy has been observed to be more effective when given before radiation in lung cancer, and head and neck or gynecologic tumors: fibrosis and damage to the vasculature by radiation have been offered as the potential explanations for the loss of effectiveness. Furthermore, using chemotherapy prior to radiation allows the identification of tumor sensitivity to drugs and their potential use for possible maintenance. Nevertheless, care must be taken to avoid an excessive toxicity and to deliver an adequate full course of irradiation without jeopardizing the benefits of a locally effective treatment.

One interesting approach consists of alternating courses of chemotherapy and radiotherapy. For example, Arcangeli *et al.* [58] used three daily fractions of radiation combined with a three-drug program (cyclophosphamide, adriamycin and methotrexate). Radiation was given on days 1 and 2 (12 Gy in 6 fractions) and repeated every week for a total of 48 Gy in 4 weeks. Chemotherapy was given the day after the first course of irradiation and repeated every 3 weeks. This program yielded a response rate of 74%, with a median survival of 46 weeks. Future studies are still mandatory, but it must be remembered that combining different modalities could lead to an undesired increase in treatment-related complications [59].

Half-body irradiation (HBI). This technique was developed empirically to treat patients with symptomatic widespread cancer. This often produced a rapid symptomatic improvement and also objective tumor responses [60, 61]. The sequential irradiation of both halves of the body is possible when a rest period of 4–6 weeks is provided for hematological recovery. The main limitation of HBI is normal lung tolerance; radiation pneumonitis from this unusual delivery can be fulminating and fatal; the reaction occurs 2–4 months after treatment and is almost invariably irreversible. The Toronto experience indicates a very sharp threshold dose for this complication with doses above 8 Gy [62]. Within this limitation, doses $\leqslant$8 Gy can achieve a 1–3 log cell kill, which could well substitute for a cycle of an active systemic drug combination.

The encouraging results obtained in pilot studies have led to several clinical trials trying to explore the role of the HBI technique in lung cancer, particularly for small cell cancer [63, 64]. In a randomized trial HBI was compared to three-drug combination chemotherapy (cyclophosphamide, lomustine and methotrexate) in small cell cancer. The radiotherapy program included two courses of HBI with 8 Gy separated by 6 weeks of rest and with a lung shield introduced at 6 Gy; a boost of 35 Gy was later delivered to the primary tumor. The response rate (88%) and the median survival for limited disease (42 weeks) were similar for both treatments. However, in extensive disease chemotherapy was largely superior, with a median survival of 44 weeks compared to 15 weeks for the irradiated group; these findings mainly reinforce the limitations in cell kill by a single dose of HBI (Table 4) [65].

In other pilot studies, when upper HBI was tried as a consolidation technique after a high-dose induction chemotherapy (cyclophosphamide, lomustine and methotrexate) it became impossible to give maintenance chemotherapy and thus the technique yielded a poor survival outcome, whereas it was highly effective after moderate doses of chemotherapy [64, 66]. In an ECOG study on non-small cell lung cancer sequential HBI did not improve survival or patterns of failure, but was associated with an increase of late radiation damage in a small number of treated patients [67]. On the other hand, an earlier pilot study of the University of

Table 4. Sequential hemibody RT for small cell lung cancer

	[65] Randomized trial		[63]	[66] High-dose chemot.
	H.RT	Chemot.	H.RT	upper H.RT
Limited disease				
CR*	11/17	8/19	-	5/8
PR	5/17	9/19	-	3/8
Median survival (days)	304	302	-	360
Extensive disease				
CR	3/13	7/15	5/19	1/4
PR	7/13	6/15	6/19	3/4
Median survival (days)	159	307	119	157

*CR = complete response; PR = partial response; H.RT = hemibody irradiation; Chemot. = chemotherapy.

Rochester using sequential HBI plus loco-regional fields indicated a delay but no prevention of metastatic spread in advanced non-metastatic non-small cell lung cancer when compared to retrospective controls treated by split-course irradiation alone [63]. In its present form, HBI is still controversial. However, the technique must not be discarded since further testing is necessary and new approaches are emerging, such as fractionation of the HBI technique and its potential combination with radiosensitizers or radioprotectors.

Prophylactic brain irradiation. An analysis of the failure in lung cancer stresses a high incidence of brain metastases. In an autopsy series the incidence varied from 13% for squamous cell carcinoma to 54% for adenocarcinoma. The most interesting observation was that brain metastases were the only site of failure in 6% of patients with small cell carcinoma and 12% of adenocarcinomas [68]. Numerous studies have demonstrated the effectiveness of prophylactic whole-brain irradiation in small cell lung cancer [69]. For other histologic types, only one randomized trial is available: the incidence of brain metastases was reduce when 20 Gy were given to the whole brain, particularly in patients with adenocarcinoma (4/18 patients vs 1/16 patients), but this difference was not statistically significant [68]. It has been stated that although elective whole-brain irradiation decreases the incidence of metastatic spread to the brain in small cell carcinoma, it does not affect survival [69]. Future improvements in the control of the primary tumor and other metastatic sites will clearly outline the necessity for a CNS radiation-prophylaxy.

At the present time the treatment of patients with advanced lung cancer is still very frustrating; only a small proportion of patients can be cured by radiation. The major contribution of radiation therapy has been in achieving loco-regional tumor control. All efforts should be made to increase this local effectiveness of radiation, but also to decrease its potential late damage. Furthermore, most forms of lung cancers, even when only locally advanced, are in fact subclinically disseminated. This dictates an additional need for an effective systemic treatment. It is important to emphasize that care must be taken with these approaches in order to not outweigh the expected benefits by causing an increase in morbidity and/or a deterioration in the patient's quality of life.

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