

The Evolving Role of Radiation in Pancreatic Cancer



Evan Landau, MD^{a,*}, Shalom Kalnicki, MD, FACRO^b

KEYWORDS

• Pancreatic cancer • Radiation • Chemoradiation therapy • SBRT • SABR • IMRT

KEY POINTS

- The role of radiation in pancreatic cancer is still evolving.
- The data supporting this modality are mixed and likely reflect the systemic nature of this disease.
- Using the correct patient selection, in combination with the newer radiation technology, a role for radiation likely still exists.

Pancreatic cancer is an aggressive malignancy with a poor long-term survival and only mild improvement in outcomes over the past 30 years. Local failure remains a problem and radiation can help improve control. The role of radiation therapy in pancreatic cancer has been controversial and is still evolving. This article reviews the trials of pancreatic cancer and radiation in adjuvant, neoadjuvant, and unresectable lesions. The article reviews the impact and outcomes of evolving radiation technology.

ADJUVANT CHEMORADIATION

The benefit of chemoradiation therapy (CRT) following a pancreatic resection is unclear. There have been 3 randomized trials with conflicting outcomes. The first randomized trial performed by Gastrointestinal Tumor Study Group (GITSG) showed a survival benefit with split-course radiation and 5-fluorouracil (5FU) chemotherapy.¹ A confirmatory trial showed no survival benefit for CRT compared with observation.² The most recent data are from a phase 3 randomized trial performed by the European Study Group for Pancreatic Cancer (ESPAC) using a complex 2 by 2 factorial design trial that randomized postresection subjects to 4 arms: observation, 5FU, 5FU plus

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^a 21st Century Oncology, Broward Health, 1625 Southeast 3rd Avenue, Fort Lauderdale, FL 33316, USA; ^b Radiation Oncology, Montefiore Medical Park, 1625 Poplar Street, Bronx, NY 10461, USA

* Corresponding author.

E-mail address: evan.landau@21co.com

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split-course radiation, and 5FU plus split-course radiation therapy followed by 5FU. The trial found that chemotherapy improved projected 5-year survival to 21% versus 8% in the non-chemotherapy arm ($P = .009$). The CRT arm was inferior to the non-CRT arm with a 5-year survival of 10% versus 20% ($P = .05$), respectively.³ Attempts to combine radiation with gemcitabine using modern radiation techniques have not shown a survival benefit for radiation.⁴ Only a single randomized trial from the 1980s showed a survival benefit to CRT, with recent data showing either no benefit or a detriment.

These trials have been criticized for multiple reasons. All 5FU trials used a now antiquated split-course of radiation with a planned 2 week hiatus, which may be inferior in to the current sequential treatment. In addition, the ESPAC trial, had a complex 2 by 2 factorial design, no quality assurance of radiation therapy planning, and field size and technique were not standardized, which may explain the poor CRT outcomes. A subsequent (Radiation Therapy Oncology Group [RTOG] 97-04) report confirmed that the radiation quality affects survival.⁵ Finally, current treatment differ vastly from the randomized trials designed in the 1980–1990. All of these phase 3 trials utilized two dimensional x-ray based targeting with limited motion management, poor image guidance and antiquated radiation planning, and as such raises questions of applicability to modern treatment.

As multiple critiques have been raised, some have pointed to retrospectives series as support for adjuvant CRT. A John Hopkins series of 908 subjects status postpancreatectomy showed a nearly 7-month median survival benefit in CRT (21.2 vs 14.4 months, $P < .001$).⁶ In addition, similar findings were shown in a cohort of 472 subjects, with a 25.5-month versus 19.2-month median survival benefit ($P = .001$).⁷ These conflicting data have influenced current guidelines. The National Comprehensive Cancer Network favors chemotherapy alone or induction chemotherapy followed by CRT. The European Society for Radiotherapy and Oncology guidelines do not recommend adjuvant CRT.⁸ The RTOG 08-48 is currently accruing subjects for a trial testing 6 months of adjuvant induction chemotherapy and randomization to CRT versus observation in stable subjects. This trial uses modern techniques and has a computed tomography (CT)-based atlas to ensure appropriate target delineation (available at <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0848>).

Unresectable Pancreatic Cancer

Thirty percent of patients have locally unresectable pancreatic cancer at diagnosis⁹ and overall mean survival is limited to 13.6 months.¹⁰ The best management is controversial.

Concurrent chemotherapy and radiation

The benefit of concurrent CRT is controversial because of conflicting trial outcomes. Two initial trials compared antiquated concurrent chemotherapy and radiation versus chemotherapy alone. The GITSG trial of 43 subjects with locally advanced pancreatic cancer (LAPC) showed the combination 5FU and 54 Gy of radiation showed an improved 10-week survival but toxicity in the CRT was “severe” in 50% of patients.¹¹ In 1985, a study of LAPC patients of 5FU versus 5FU and 40 Gy radiation, and showed no benefit of CRT with nearly identical median survival.¹²

After the acceptance of gemcitabine as standard chemotherapy, 2 CRT versus chemotherapy trials were published, again with different outcomes. The Federation Francophone de Cancerologie Digestive (FFCD) group randomized LAPC subjects to a high dose of radiation of 60 Gy with infusional 5FU and intermittent cisplatin

versus gemcitabine alone. This trial showed a statistically significant decrease in median survival with CRT of 8.6 months versus gemcitabine alone of 13 months ($P = .03$). This trial has been criticized for the high dose of radiation and combination regime which was not previously tested, poor compliance with treatment, and high CRT toxicity of 78% grade 3 or 4.¹³ Eastern Cooperative Oncology Group (ECOG) randomized LAPC subjects to full-dose gemcitabine alone versus CRT with 3D CT and dose-reduced gemcitabine (600 mg/m²). The trial was closed early secondary to poor accrual but was still powered to show a survival benefit in the CRT arm of 11.1 to 9.2 months ($P = .017$). However, toxicity was high in CRT arm with 41% at grade 4 or 5.¹⁴

Which chemotherapy with radiation: concurrent capecitabine–5-fluorouracil or gemcitabine?

The initial CRT trials used 5FU-based chemotherapy as the radiation sensitizing agent. However, gemcitabine has become a standard due to significant systemic efficacy and improved survival.^{15,16} In addition, it is a potent radiation sensitizer,¹⁷ although initial experience noted significant toxicity when combined with radiation.¹⁸ Even in the phase III setting, the combined approach has yielded many side effects. Multiple studies have consistently demonstrated success with both acceptable toxicity and encouraging overall survival with gemcitabine as a radiation sensitizer, with some trials using a full-dose regime.¹⁹

The SCALOP trial addressed the question of which concurrent agent is better. The investigators successfully treated 114 subjects with LAPC to induction chemotherapy, then randomized the subjects to combination gemcitabine and radiation or capecitabine and radiation. There was no statistical improvement in the capecitabine arm, with overall survival of 17.6 months versus 14.6 months in the gemcitabine arm ($P = .185$); however, the per treatment and multivariate analysis found a benefit to capecitabine and radiation.²⁰ In addition the hematologic side effects rate was higher in the gemcitabine arm and, in both arms, only 68% to 74% of subjects completed the total radiation dosing.²¹

LAP07 (Chemoradiation vs Chemotherapy Trial)

The findings from a Groupe Coopérateur Multidisciplinaire en Oncologie or GERCOR induction chemotherapy study led to most recent and influential CRT versus chemotherapy trial, the LAP07.²² This 2 by 2 French trial randomized subjects to 2 induction options: gemcitabine (1000 mg/m²) versus gemcitabine (1000 mg/m²) plus 100 mg/d of erlotinib. Of the subjects, 442 were randomized to chemotherapy and 269 subjects did not progress after the 4 months induction period and were randomized to same-dose chemotherapy versus 54 Gy plus capecitabine. The radiation was 3D CT-based without prophylactic lymph node irradiation but with a sizable margin of 3 cm superior to inferior. In the final analysis, no survival benefit was found with the addition of radiation. A 14% local control benefit was noted and the CRT had a similar toxicity to chemotherapy except for more nausea.¹⁰ This trial has had a significant impact on the national guidelines. The American Society of Clinical Oncology guidelines consider chemotherapy as the standard with CRT if no progression is noted.²³

Who should get radiation based off the trial outcomes?

Based on the mixed and equivocal data of radiation therapy in the adjuvant and LAPC setting, the benefit and role of radiation in pancreatic cancer is uncertain. The authors hold that radiation therapy has a role in pancreatic cancer for several reasons. First, patient selection strongly influences outcome; second, the anatomic complexity and

motion of the pancreas during treatment may explain some of the mixed data; third, new technology may offer better therapy and improved outcomes; and, finally, using this new technology for neoadjuvant chemoradiation may be the preferred treatment application.

Patient selection

Distant failure is all too common in pancreatic cancer, and local treatment should only be offered to patients with local disease or a local failure pattern. Upfront chemotherapy may help stratify risk and has become the recommended standard of care in LAPC.²³ The rationale for this standard is compelling. First, pancreatic cancer has a high metastatic rate and nearly a quarter of LAPCs will have rapid distant progression during the initial course of treatment.¹⁰ Therefore, systemic therapy should be offered early in the course of management. Second, CRT has toxicity and should only be offered to patients who have been shown to have local disease. Finally, chemotherapy is effective¹⁵ and it may make the target more receptive and amenable to radiation. Clinical data support this approach. The MD Anderson group looked at a retrospective analysis of their patients who underwent induction chemotherapy followed by CRT, versus CRT alone. They found a 3-month survival improvement in the induction group.²⁴ In a subgroup analysis of multiple prospective phase II and III GERCOR group studies, a comparison of CCR induction chemotherapy followed by CRT versus chemotherapy alone also yielded a survival benefit in the induction group.²²

Predicting local failure: SMAD4 Gene and CA19-9 Tumor Marker

Local failure remains a significant problem in pancreatic cancer. In 3 cited studies using chemotherapy alone, it ranged from 34% to 46%. Ideally, radiation should be offered to patients when preventing local failure might affect survival. SMAD4 (dpc4) is a histologic marker that has been shown to correlate with failure pattern. In a rapid autopsy series dpc4 was highly correlated with metastatic disease.²⁵ In a phase 2 trial examining the benefits of Erbitux, with induction chemotherapy and then with concurrent chemoradiation, a secondary analysis on SMAD4 mutation showed that an intact SMAD4 was associated with an increased risk of local progression, whereas loss of SMAD4 was associated a distant dominant progression.²⁶ However, the predictive failure pattern of SMAD4 in post-Whipple cases is uncertain.^{27,28}

Questions remain about the application and predictability of SMAD4 because the local patterns of recurrence may not correlate with the usual radiation field. An additional difficulty may exist because needle biopsy may provide insufficient sampling for SMAD4. One study of preoperative cytology, via Endoscopic Ultrasound Guided Fine Needle Aspiration, incorrectly classified the SMAD4 in 29% of the sample compared with the final pathologic results.²⁹

Ca19-9 a marker used to predict survival in pancreatic cancer³⁰ has been suggested as a risk stratifier following induction chemotherapy. In the SCALOP trial, a Ca19-9 following induction chemotherapy and before chemoradiation of less than 46 U/mL was associated with improved survival at 12 months; therefore, patients with a Ca19-9 below may be better candidates for subsequent chemoradiation.²⁰

Anatomic complexity and motion

Pancreatic cancer offers multiple complexities in the successful administration of radiation treatment and the initial radiation technology was limited in meeting these challenges. First, the pancreas is anatomically adjacent to multiple organs sensitive to radiation, including the kidneys, liver, stomach, and small bowel, as well as, in particular, the duodenum. Therefore, for radiation therapy to be successful the dose must be

sculpted to the cancer and excess radiation to the normal adjacent organs avoided. This was not available in older trials, which used 2D targeting and limited organ sparing. Second, the pancreas is a moving target and during 1 respiratory cycle moves 1.5 to 3.5 cm.^{31–33} Therefore, to cover the target during the respiratory cycles, early series added a motion margin of 2 cm to 3 cm.^{10,13} Increasing the margin may allow better coverage of the target but with increased treatment morbidity. This may partially explain the high toxicity rate in early papers on ablative radiation in which a larger margin was used and the late grade 2 morbidity was 94%.³⁴

New technology

Radiation has benefited from multiple technological innovations during the past 15 years, which may combat some of these issues. Significant progress has been made in reducing the target size. Modern external radiation treatment benefits from real-time image guidance, which includes daily conebeam and kilovoltage (kV) imaging. This technology allows for accurate daily matching and decreases in target margin. In addition, better preradiation 3D-imaging technology provides more accurate tumor delineation.

Smaller Targets: Avoiding Elective Nodal Irradiation

The radiation target in pancreatic cancer has also changed. Typically, nodal groups and the primary tumor were included in the radiation field because regional nodes are involved in at least 30% of pancreatic cancer.³⁵ However, as radiation doses escalated, nodal irradiation was deemed too morbid. Most new series of radiation of pancreatic cancer avoid elective lymph node irradiation and only target tumors.^{19,36} In addition, patterns of failure series have helped better define the peripancreatic area as the site of greatest risk.³⁷ Finally, and somewhat provocatively, without elective nodal irradiation tumor control is consistently better, or as good as, when electively nodes were included in radiation treatment. This brings up the question of whether there is any benefit to elective nodal treatment at all.

Dose Sculpting

Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) is a technology that divides radiation into small beamlets and shapes them around the target to improve sparing of adjacent organs. In addition, complex planning algorithms are used to maximize therapy. Efforts have been made to utilize this technology as a means of increasing the dose of radiation and avoiding toxicity.³⁸

Gemcitabine is a potent radiation sensitizer¹⁷ but early combinations with radiation led to high toxicity. A dose escalation trial in unresectable subjects that used IMRT concurrent with gemcitabine (1000 mg/m²) delivered 55 Gy in 25 fractions showed an encouraging 24% resectability rate and a 14.8-month overall survival.¹⁹ A confirmatory retrospective series indicated a mean overall survival of 22.9 months and a resection rate of 29%.³⁹ In addition, IMRT has lessened the toxicity versus 2D or 3D technology.³²

An MD Anderson group published a provocative concept of treating LAPC with induction chemotherapy and hypofractionated IMRT. IMRT was used to create hotspots of dosage in the tumor and spare the adjacent organs by respiratory motion management.⁴⁰ They compared it to the standard dose and found a better 3-year survival of 31% versus 9%.⁴¹ This concept was adopted for a prospective phase II RTOG trial that was terminated because of slow accrual (available at <https://www.rtog.org/LinkClick.aspx?fileticket=HQpVTI4rE58%3D&tabid=290>).

Stereotactic Body Radiation Therapy or Stereotactic Ablative Radiation

Stereotactic body radiation therapy (SBRT) has shown much promise in pancreatic cancer and is rapidly setting a new standard. SBRT technology uses high doses of radiation per fraction (>6 Gy) and fewer fractions (1–5) in a conformal radiation field.⁴² The pancreas as a target for ablative radiations offers several challenges. The lesions are adjacent to radiation sensitive organs, particularly the duodenum, and the pancreas is a moving target because of respiratory motion.³³ Technology has been developed to combat this issue. Motion management via either robotic hybrid tracking technology with fiducial markers or with linear accelerator-based abdominal compression, gating, and image guidance have been effective, and have reduced the set up margin from 2 to 3 cm to 2 to 3 mm.⁴³

Stereotactic body radiation therapy prospective data

The SBRT literature is limited, without phase III studies, and has only a few prospective or phase II studies. Early publications showed excellent local control (>90%)⁴⁴ but concerns about late grade 3 toxicity greater than 33%.³⁴ Toxicity has been lowered by adopting a 5 to 6 fraction course. A recent publication showed a 2-year local recurrence rate of 90% and no grade 3 toxicity.⁴⁵ These treatments can be completed in a week and all full-dose systemic therapy can be continued. Finally, SBRT has shown progress in borderline resectable subjects. One retrospective study of 101 subjects treated with gemcitabine, docetaxel, capecitabine, and SBRT showed that 54.5% underwent resection, 96.4% had complete resection (R)-0, and there was a 33-month survival for resectable subjects (Table 1).⁴⁶

Stereotactic body radiation therapy versus intensity-modulated radiation therapy

There are no comparative studies between IMRT using 25 to 28 treatments versus the SBRT 1 to 5 fractions. The prolonged treatment with IMRT allows for the integration of systemic chemotherapy as a sensitizer but may delay full-dose chemotherapy. SBRT allows for a short course but it is not sensitized by chemotherapy and, because it uses an ablative dose in its therapy, it may be limited by the risk of adjacent small bowel damage. SBRT may allow for a smaller target volumes as in one series the SBRT target was 1/3 the size of the standard CRT treatment.⁴⁷ Wild and colleagues⁴⁸ suggested that the larger radiation field and additional fractions of IMRT may have an associated morbidity because significantly increased amounts of circulating blood lymphocytes are irradiated. These lymphocytes may be active in tumor kill, and lymphopenia was found to be a prognostic finding in CRT pancreatic subjects (Tables 2 and 3).

Future developments: stereotactic body radiation therapy and immunotherapy

SBRT may offer tumor-related immunogenic modulation that may not be found in CRT cases. SBRT has been associated with a host of changes in the tumor

Table 1 Stereotactic body radiation therapy for unresectable cancer					
Trial	N	Dose	FFLP	Overall Survival	Toxicity (Late)
Rashid et al, ⁴⁶ 2016	49	6.6 Gy/5 fx	78% at 1 y	13.9 mo	10.6% > grade 2
Chang et al, ³⁶ 2009	77	25 Gy/1 fx	84% at 1 y	11.9 mo	25% > grade 2 9% > grade 3
Comito et al, ⁴⁵ 2017	45	45 Gy/6 fx	90% at 2 y	19 mo	4% > grade 2 0% > grade 3

Abbreviation: fx, fractions of radiation treatment.

Table 2

Induction chemotherapy: 3-Dimensional Chemoradiation Therapy versus Intensity-Modulated Radiation Therapy versus Stereotactic Body Radiation therapy for Unresectable Pancreatic Cancer

Trial	Induction	Concurrent Chemotherapy and Radiation Technique	N	Overall Survival Median	Toxicity grade 3	FFLP	Surgery Rate
LAPC07 ¹⁰	Gemcitabine	Capecitabine 3D Radiation	109	15.2	24%	—	4%
Ben Josef et al, ¹⁹ 2012	Gemcitabine	Gemcitabine IMRT	50	14.8	24%	59% at 2 y	20%
Herman et al, ⁶ 2015	Gemcitabine	SBRT	49	13.9	6%	78% at 1yr	8%

Abbreviations: FFLP, freedom from local progression; SBRT, Stereotactic body radiation therapy.

microenvironment that can be presented to the immune system, including release of tumor debris, inflammatory cytokines, and tumor associated antigens. This response has been shown in vivo models to be dose-dependent and ablative dosing of SBRT may lead these tumor cells to function as an antitumor vaccine.⁴⁹ This combination approach is currently being tested in multiple prospective trials.⁵⁰

Dose escalation

In general, curable dosing of gross disease is normally in excess of 70 Gy but most past series have limited dosing to 40 to 50 Gy. Early efforts in dose escalation have met significant toxicities^{34,51} and no outcome improvement.^{13,52} These initial failures may reflect toxicities from poor technique. However, in recent literature there are suggestions that increases in dosing may lead to better local control. The IMRT escalation studies have shown encouraging improvement in outcome and local control with some morbidity.¹⁹ Two retrospective comparison studies showed survival benefit with dose escalation.^{41,53} Ablative dosing with SBRT, in both single fraction and multiple fraction, has excellent local control.⁴⁵ In addition, intraoperative radiation allows for organ-sparing dose escalation and has demonstrated encouraging results.⁵⁴

Neoadjuvant Chemoradiation

The best option for cure for a patient with pancreatic cancer is a surgical excision. However, only a small subset of all patients present with resectable disease;

Table 3

Intensity-modulated radiation therapy versus stereotactic body radiation therapy linear accelerator or robotic radiosurgery

	IMRT	SBRT Liniac/Robotic Radiosurgery
Number of treatments, length	25–28, 5–6 wk	1–5, 1 wk
Dosing	45–50 Gy	25–33 Gy
Chemotherapy	Concurrent	Sequential
Image guidance	Conebeam	Conebeam or KV-hybrid tracking
Respiratory management	Abdominal compression gating	Abdominal compression gating fiducial tracking
Target size	300–500 mL	100 mL
Elective nodal treatment	Can allow	Very limited

therefore, this cure option is not available to most patients. In addition, even among patients with resectable cancer at presentation, the cure rate is limited and the rate of positive margins at surgery is common with a R1 resection rate of 17% to 42%. Finally, surgery can be associated with significant morbidity and a significant percentage of patients develop metastatic disease rapidly after surgical excision. The benefit of adjuvant therapy has been primarily flat during the past 25 years. This has led many investigators to pursue a neoadjuvant approach of chemotherapy and radiation.

This approach may offer multiple theoretic advantages. First, nonsurgically manipulated tissue may allow for a better vascular supply to the tumor and possibly a higher response rate to induction chemotherapy and radiation. Second, this approach may shrink the size of the tumor and improve resectability, R0 resection, and lymph node sterilization. Third, this technique allows investigators and clinicians to assess the response to the tumor. Fourth, a delay in systemic therapy may lead to rapid progression of distant metastatic disease. However, questions remain.

Does neoadjuvant therapy in fact improve the resectability and is it better than upfront resection?

Prospective phase II trials have shown encouraging outcomes with neoadjuvant approach. The resectability rate was improved in a heterogeneous metaanalysis of 111 subjects, by 73% for resectable cancers and 33% for LAPC or borderline cases.⁵⁵ In addition, the R0 resection rate has been reported to be high following neoadjuvant therapy. A metaanalysis of subjects with neoadjuvant gemcitabine-based therapy showed an improvement of 89% in resectable and 60% in unresectable patients.⁵⁶ In resectable patients a phase II trial of 86 patient who underwent a Gemcitabine (400mg/m²) CRT showed that 13 patients progressed, and 73 underwent surgery, the overall population had an encouraging 22.7 months median survival.⁵⁷ In a large phase II trial of 188 resectable subjects treated with neoadjuvant gemcitabine (1000 mg/m²) with fractionated 50 Gy in 25 fractions yielded a resection rate of 87%, an R0 of 99%, and a very encouraging 5-year survival of 57%.⁵⁸ Similar findings were reported in a smaller US multi-institutional series.^{12,59}

The question of whether neoadjuvant or adjuvant therapy is the better approach can only be answered in a randomized trial. One randomized trial was attempted and failed to accrue subjects. Some retrospective data suggest a benefit to neoadjuvant treatment. In a single retrospective comparison of borderline or LAPC subjects undergoing FOLFIRNOX (fluorouracil [5-FU], leucovorin, irinotecan and oxaliplatin) plus or minus radiation, the 50% who had surgery versus an upfront surgical series showed an improved outcome with the neoadjuvant approach, a decrease in margin positivity, lower lymph node positivity, and lower operative morbidity.⁶⁰ A second retrospective comparison series between resectable subjects undergoing upfront surgery versus neoadjuvant chemotherapy and SBRT showed a decrease in positive margins, similar morbidity and improved survival of 33.5 vs 23.1 months, ($P = .057$).⁶¹ In addition, a population-based study of operable pancreatic cancer found an improvement in survival for neoadjuvant versus adjuvant treatment.⁶² However, these data may reflect a selection bias in favor of the neoadjuvant patients because the patients who progressed during neoadjuvant were not included.

Does neoadjuvant therapy allow for the clinician to assess response?

Neoadjuvant therapy likely offers a histologic response; however, radiographic changes may be limited. In a large metaanalysis of 111 studies, the investigators reported that combined radiographic and histologic response rate was 33%.⁵⁵ In

addition, histologic responses on surgical pathologic reports have been shown to be high at 50% in a series.⁶³ However, recent data cast doubt on the benefit of neoadjuvant treatment to yield a radiographic change. A single institution experience of subjects with borderline resectable cases treated with neoadjuvant CRT only yielded a radiographic change in less than 1% of subjects.^{12,64} A similar study of 40 subjects undergoing neoadjuvant treatment showed that radiographic findings may show a decrease in tumor size but radiographic downstaging was unreliable.⁶⁰ In the SBRT literature, the response rate can be high but significant radiographic regression may not be noted.⁴³ These finding may reflect CTs inability to differentiate tumor from fibrosis; in 1 surgical series a 56% fibrosis rate was noted following neoadjuvant therapy.⁶⁵

SUMMARY

The role of radiation in pancreatic cancer is still evolving. The data supporting this modality are mixed and likely reflect the systemic nature of this disease. Using correct patient selection in combination with the newer radiation technology, a role for radiation likely still exists.

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