Management of Lymph Node–Positive Prostate Cancer: The Role of Surgery and Radiation Therapy

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Current evidence for the management of lymph node–positive prostate cancer suggests both a disease-control and survival benefit to systemic ADT plus surgery and radiation.

Introduction

Prostate cancer (PCa) is the most common malignancy in men. In the United States, one out of six men will be diagnosed with prostate cancer during their lifetime.[1,2] Because of stage migration during the prostate-specific antigen (PSA) era, the vast majority of patients with newly diagnosed PCa have clinically localized disease, defined by the absence of nodal or distant metastases. In the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, out of 12,000 patients diagnosed between 1990 and 2004, only 2.4% presented with bony metastatic disease (M+) at their initial diagnosis.[3] There are no recent data on initial presentation with radiographically evident lymph node–positive (LN+) disease in the absence of bony metastases. The current (7th) edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual groups M+ and LN+ disease together as stage IV.[4] Many physicians tend to view these two categories of patients as having similar outcomes, and approach their treatment with the same algorithm.

FIGURE 1


The goal of this article is to review the data on management of PCa with lymphatic involvement (LN+) and focus on the role of multimodality therapy, which combines systemic and local therapies in managing these patients. Patients with LN+ PCa can be broadly separated into two groups, largely based on the bulk of nodal disease. Patients who undergo staging scans prior to surgery and have no radiological evidence of pelvic lymphadenopathy but are then found to have involved pelvic lymph nodes at the time of pelvic lymph node dissection (PLND) have pathologically node-positive (pN+) disease, and they are considered to be in the favorable category. This is in contrast to clinically node-positive (cN+) patients, who have pathologically enlarged lymph nodes on staging scans and in whom surgery is rarely even attempted. According to the 2013 National Comprehensive Cancer Network (NCCN) guidelines,[5] patients with metastases to the lymph nodes by imaging studies (cN+) should be treated systemically with androgen deprivation therapy (ADT) or radiation therapy (RT) with long-term ADT, and patients with involved lymph nodes detected at the time of radical prostatectomy (pN+) are offered observation, ADT, or RT with long-term ADT (Figure 1). While ADT is the common denominator, there is no consensus on the role of local therapies in management of patients with LN+ PCa.

Management of Microscopic LN+ PCa, as Determined at PLND (pN+)

The incidence of nodal metastases in patients with presumed clinically localized PCa decreased from rates of 20% to 40% in the 1980s[6,7] to rates of 4% to 6% in the most recently published reports,[8-10] again likely due to stage migration in PCa during the PSA era. Indeed, the Mayo series revealed a marked decline in the incidence of positive lymph nodes at the time of radical
prostatectomy (RP), from 9.1% between 1988 and 1993 to 1.8% between 1998 and 2001.[11] Traditionally, involvement of regional lymph nodes in PCa was regarded as a poor prognostic factor, indicating systemic disease with limited long-term survival regardless of treatment. In the European Organisation for the Research and Treatment of Cancer (EORTC) Genito-Urinary Group protocol 30846, launched in 1986, RP was aborted if lymph node involvement was found during PLND, and men were randomized to either immediate or delayed ADT, which consisted of a 3.6-mg 1-month depot of the luteinizing hormone-releasing hormone (LHRH) agonist goserelin (Zoladex) combined with 50 mg of the antiandrogen cyproterone acetate three times daily during the first 4 weeks, for flare prevention. Orchiectomy was also allowed in lieu of medical castration. In the delayed-treatment arm, treatment was started at disease progression, defined as development of bone metastases, new lymph node or soft tissue metastases, or a 30 cc or greater increase in primary tumor volume. At the time of progression under endocrine treatment in each arm, further treatment was left to the discretion of the investigator but the continuation of endocrine treatment was suggested. At a median follow-up of 9.6 years,[12] the time to death in patients with LN+ PCa (median 6.2 and 7.8 years with delayed vs immediate treatment, respectively) was greater than that in patients with M+ disease (median 2.5 years, based on a contemporary meta-analysis by the Prostate Cancer Trialists’ Collaborative Group).[13] The update of the EORTC 30846 trial with a 13-year follow-up revealed that approximately 60% of deaths on both arms were due to PCa.[14] This trial provides a good benchmark for the natural history of pN+ PCa in the absence of local therapy.

The Role of Radical Prostatectomy in Management of pN+ PCa

Although direct comparison of different trials is a flawed approach, their collective results do provide interesting insights. At the same time as the EORTC was enrolling patients on protocol 30846, the Eastern Cooperative Oncology Group (ECOG) launched a randomized trial of immediate vs deferred ADT in patients who were found to have pathologically involved lymph nodes at the time of RP, but in contrast to the EORTC trial, these patients underwent RP and were randomly assigned to receive immediate, continuous ADT (3.6 mg of goserelin monthly or bilateral orchiectomy, by patient choice), or to be followed up and receive ADT when clinical recurrence was detected (not counting events with only detectable or rising PSA concentrations). With a median follow-up of 11.9 years,[15] median overall survival (OS) was 13.9 vs 11.3 years in the immediate-ADT and delayed-ADT groups, respectively. In the immediate-ADT group, 41% of patients died of PCa compared with 89% in the delayed-ADT group.

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<th>Outcomes for Patients Treated With Various Combinations of Androgen Deprivation Therapy and Local Therapies for Lymph Node–Positive Prostate Cancer</th>
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Other surgical series have been published, and outcomes from selected studies are summarized here as well as in the Table. Frohmuller et al[16] published their series of 139 patients treated with PLND at the University of Wrzburg between 1969 and 1992. In this group, 87 patients received ADT alone and 52 received RP with ADT. The great majority of these patients were not staged with pelvic imaging prior to surgery. With a short follow-up of 4.5 years, the actuarial OS rates, prostate cancer–specific survival (PCSS), and progression-free survival (PFS) at 10 years were in favor of radical prostatectomy. The groups were heavily unbalanced by nodal disease bulk. Among patients

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in the RP + ADT group, 75% were staged as pN1 and 25% as pN2, whereas in the ADT-alone group 25% were staged as pN1 and 75% as pN2. However, the importance of this publication is in a detailed analysis of local tumor progression in the two groups of patients. Local disease progression occurred in 60 of the 87 (69%) patients who had not undergone radical prostatectomy. Because of clinically significant symptoms associated with local disease progression, such as urinary retention or bleeding, surgical intervention was necessary in 29 of these 87 patients (33%). Of these 29 patients, 18 required a single transurethral resection of the prostate (TURP) and 11 required multiple TURPs. In contrast, in the RP+ADT group, 4 patients out of 52 (8%) developed a local recurrence, but none required surgery; one patient after RP required urethral dilatation due to a stricture at the level of the vesicourethral anastomosis. Due to group imbalances and lack of robust statistical adjustment for these imbalances, comparison of outcomes in the two groups is challenging, but knowledge of the natural history of primary disease and the importance of local control, despite systemic progression, are emphasized by this publication.

A larger Munich Cancer Registry series[17] of 938 patients accounted for such imbalances in their statistical methods. Although cases were not matched, random samples were generated. In this series, 688 patients were similarly treated with RP after PLND revealed LN+ disease, whereas 250 were treated without RP. About 75% of all patients received adjuvant ADT and 25% received adjuvant RT, with adjuvant therapies equally balanced between the two groups. With a median follow-up of only 5.6 years, OS was significantly better in the RP group, and after adjustment for age, clinical T stage, number of positive lymph nodes, World Health Organization (WHO) grade, and PSA level, patients who underwent RP were more likely to be alive, with a hazard ratio (HR) of 2 (95% confidence interval [CI], 1.6–2.6). A large Mayo series[11] of RP in 507 LN+ patients at the time of PLND, with the longest follow-up being 10.3 years, revealed a 10-year PCSS of 86%, with 56% of men free from biochemical recurrence at the time of their last follow-up visit. In this series, 90% of the patients received adjuvant ADT and 9% received adjuvant RT. On multivariate analysis, Gleason score 8–10, positive surgical margins, and two or more positive lymph nodes were adverse predictors of PCSS, whereas adjuvant ADT use was not associated with systemic progression or cancer-specific survival. A meticulous PLND with no adjuvant therapies produced intriguing results in a publication by Bader et al.[18] A total of 88 patients treated at the University of Bern between 1989 and 1999 were followed over a median of 3.7 years. Authors described dissection of tissues along the external iliac vein, in the obturator fossa, and along the internal iliac artery, with removal of a median of 21 lymph nodes. The projected probabilities of OS and of PCSS for these 88 patients were both 74% at 5 years. In a multivariate Cox proportional hazards model, which included the number of lymph node metastases, tumor stage, and Gleason score, the only variable affecting progression and cancer-specific death was the number of positive lymph nodes. In this study, only 8% of patients with one positive lymph node died of PCa, compared with a 25% mortality rate from PCa among patients with two positive lymph nodes and a 36% rate among patients with more than two positive lymph nodes.

Bulk of Lymphatic Involvement as a Predictor of PCa Outcome

There are no radiological data on bulk of lymphatic involvement and PCa outcome, most likely due to the rare presentation of isolated lymphatic metastases in the absence of distant metastatic disease (LN+M0). However, the available pathological data provide a meaningful insight into the relationship between the size and number of involved lymph nodes and disease prognosis. Schiavina et al[19] confirmed the association between number of positive LN+ and disease outcome. A total of 98 consecutive patients treated at the University of Bologna with RP between 1995 and 2011 were divided into three groups based on number of positive LN+ and Gleason score. Of note, 80% of these patients received adjuvant ADT and 50% received adjuvant RT, with equal rates of adjuvant therapies between the groups. With a median follow-up of 5.7 years, patients with one to three positive LN+ had PCSS at 5 and 10 years of 91% and 84%, compared with patients with more than three positive LN+, whose PCSS rates were 72% and 44%, respectively.

After finding a strong association between the number of positive LN+ and the rate of PCSS,[18] the researchers at the University of Bern looked further into the histopathological characteristics of the LN+ in 102 patients treated between 1989 and 2002 with the same meticulous PLND, as described earlier. The median diameter of the largest LN metastasis per patient was 6 mm (range, 0.3–35 mm). Initially, the authors hypothesized that the presence of extranodal extension (ENE) would independently predict survival; however, on multivariate analysis—which included cancer volume in the prostate, T stage, Gleason score, ENE, number of positive LN+, and diameter of the largest LN
metastasis per patient—only the diameter of the largest metastasis per patient ($< 6 \text{ mm vs } \geq 6 \text{ mm}$) and the Gleason score predicted survival.[20] In a subsequent analysis, the diameter of the largest metastasis (with a cut-off of 10 mm) per patient was the strongest prognosticator for all endpoints.[21] The 5-year overall, disease-specific, and relapse-free survival rates for patients with largest nodal metastases of 10 mm or less were 85%, 87%, and 33%, compared with 54%, 57%, and 18%, respectively, for patients with largest nodal metastases greater than 10 mm. The HR of 4.2 for disease-specific survival (DSS) implied a more than quadrupled risk of dying from cancer for patients with larger LN metastases. One might hypothesize from this analysis that patients who are found to have LN+ disease by imaging are likely to have outcomes similar to those of patients with larger LN metastases; that is, patients with cN+ PCa might have roughly a quadrupled risk of death from PCa compared with patients with pN+ disease determined at the time of PLND.

### The Role of Radiation Therapy in Management of LN+ PCa

The role of RT in management of patients with LN+ PCa is controversial. Many physicians use LN status as the dividing line between curable and non-curable patients, and often withhold local treatments for patients with either pN+ or cN+ PCa. Published reports, however, clearly indicate that patients live for many years after their diagnosis with LN+ PCa, and local control, either with surgery, radiation, or both, may extend their survival. This is true both in the more favorable group of patients with smaller nodal disease bulk, typically detected at the time of PLND, and in a less favorable group of patients with radiographically enlarged LNs on imaging studies. In 1976, the Radiation Therapy Oncology Group (RTOG) initiated a phase III study, RTOG 7506, for the evaluation of extended-field irradiation in locally advanced PCa. Hanks et al[22] published a 10-year outcome report on the subset of 90 patients with LN+ disease. All these patients had biopsy-proven pelvic nodal involvement, but none received RP or adjuvant ADT. In this RT-alone series, OS rates at 5 and 10 years were 63% and 29%, respectively, and PFS rates were 31% and 7%, respectively. In two patients with no evidence of disease at 10 years, PSA levels were 0.2 ng/mL and 0.8 ng/mL. Similarly, Lee et al[23] reported on a group of 36 LN+ patients treated with RT alone with a long-term follow-up of 15 years. At 5 and 10 years, OS rates were 50% and 20%, PCSS rates were 51% and 25%, relapse-free survival rates were 32% and 10%, and local control rates were 75% and 45%, respectively.

A later RTOG protocol, RTOG 8531, included 173 patients with positive lymph nodes.[24] All patients received RT and were randomized to start ADT immediately after RT or at the time of disease progression. A total of 42 patients underwent RP. With a median follow-up of 6.5 years for all patients and 9.5 years for living patients, OS at 10 years for all patients randomized to RT+ADT was 48% vs 36% for patients treated with RT and no immediate ADT. For the 131 patients who did not undergo RP, these rates were comparable at 10 years: 47% OS and 31% OS for those treated with RT+ADT vs RT alone, respectively. Biochemical control in the RT-alone arm at 10 years was 5% vs 35% in those treated with RT+ADT, and freedom from metastases at 10 years in the two groups was 67% vs 52%, respectively.

Multivariate analysis identified immediate ADT as having a statistically significant impact on all four endpoints analyzed: absolute survival ($P = .03$), disease-specific failure ($P = .014$), metastatic failure ($P = .0005$), and biochemical control ($P < .0001$). This was a retrospective subset analysis of a phase III randomized trial, and RTOG launched a subsequent randomized trial of RT with and without ADT in node-positive PCa patients in the mid-1990s. Given poor accrual, however, this trial was closed. Based on the results of RTOG 8531, immediate ADT in the setting of RT for LN+ PCa became a standard of care, in the setting of prior RP and in patients with an intact prostate. The reverse question—whether addition of RT to ADT in the setting of LN+ PCa improves outcomes—has never been studied in a randomized trial; however, several retrospective analyses can guide clinicians in this setting. Zagars et al[25] retrospectively compared the outcomes in 183 LN+ patients treated with ADT alone and 72 patients treated with combined androgen ablation and RT between 1984 and 1998 at the MD Anderson Cancer Center. None of these patients had clinical or radiographic evidence of nodal disease prior to the planned PLND, and RP was aborted if LNs were observed to be involved on frozen section.

With a median follow-up of 9.4 years, among patients treated with ADT alone, at 5 and 10 years, respectively, OS rates were 83% and 46% and biochemical failure–free survival (bFS) rates were 41% and 25%. This is in contrast to patients treated with combination of ADT and RT, in whom, with a median follow-up of 6.2 years, OS rates were 92% and 67%, and bFS rates were 91% and 80%, at 5 and 10 years, respectively. This analysis is limited by the imbalances between the treatment
arms. The median PSA in the ADT-alone group was 22 ng/mL vs 12.8 ng/mL ($P = .07$) in the combined group, and the T stage was higher in the ADT-alone group as well ($P < .01$). Therefore, the group that received ADT alone might have done worse because of more advanced disease. Nevertheless, the multivariate analysis, performed to correct for imbalances in the prognostic factors between the treatment groups, revealed that addition of RT was associated with improved outcomes, with a relative risk (RR) of 6 (95% CI, 3.1–11.5) for bFS, RR of 2.2 (95% CI, 1.4–3.4) for freedom from metastasis, and RR of 2.1 (95% CI, 1.2–3.9) for OS. Of note, patients in the RT group were treated with a four-field box technique to the prostate and periprostatic tissues only, with no pelvic node irradiation.

Da Pozzo et al.[26] published their retrospective long-term outcome data on patients treated with RP followed by either ADT alone or ADT with RT at the Vita-Salute University in Milan. This series was later combined with a series of similarly treated patients at the Mayo Clinic and formed the basis for one of the largest case-matched analyses among recent publications. This combined series[27] presented data on 703 consecutive patients with LN+ PCa treated with RP, PLND, and adjuvant treatments between 1986 and 2002 at these two academic institutions. Of all patients, 44% underwent orchiectomy, and the remaining 56% were treated with adjuvant ADT for a median of 37.5 months, with 82% of these patients receiving a combined androgen blockade. The effect of adjuvant RT was assessed using a matched analysis that allowed the authors to examine survival rates according to the type of adjuvant treatment administered (ADT with RT vs ADT alone) after adjustment for patient and tumor characteristics, such as age at surgery, pathologic T stage, Gleason score, surgical margins status, number of nodes removed, and length of follow-up. Each patient treated with adjuvant RT and ADT was matched with up to four patients treated with ADT alone. With a mean follow-up of 8.4 years, the OS rates among 117 patients analyzed in the matched population of patients receiving the combination of ADT and RT were 90% and 74% at 5 and 10 years, respectively, compared with OS rates of 82% and 55%, respectively, among 247 patients in the matched population of patients treated with adjuvant ADT alone (Figure 2). This association of adjuvant RT with improved PCSS and OS held in patients with two or fewer positive nodes and more than two positive lymph nodes.

Comparison across different treatment modalities without internal matching or adjustment for prognostic factors, such as number and size of pathologically involved LNs, is difficult. What emerges from the critical review of the literature is a growing evidence that local therapies—surgery and RT—play an important role in the management of patients with LN+ PCa. Many of these patients are alive for decades after the initial diagnosis, and achieving local control prevents salvage therapies and appears to be associated with improved rates of PCSS and OS, when combined with systemic ADT.

### Toxicity of Multimodality Therapy for LN+ PCa

The great majority of series described in this article focused primarily on oncologic outcomes rather than toxicity or quality of life. Of 98 patients treated with ADT and RT on RTOG 8531, grade 4 toxicities developed in 4.[24] These included two bowel obstructions (one with perforation), one case of cystitis, and one case of hematuria. A recently published review of toxicity outcomes of 35 patient
series, with a total of 11,835 patients treated with definitive RT for PCA,[28] revealed a median rate of late grade 2 gastrointestinal (GI) and genitourinary (GU) toxicities to be 15% and 17%, respectively. Late grade 3 and higher GI and GU toxicities were 2% and 3%, respectively. This analysis included patients who did not receive pelvic RT and who were treated in the previous era before the introduction of intensity-modulated radiation therapy (IMRT), so it can provide only limited guidance to patients and clinicians when discussing toxicity outcomes with multimodality therapy for LN+ PCa.

Toxicity data can be extrapolated from three recently published randomized trials of adjuvant RT vs observation for patients with adverse features after RP: Southwest Oncology Group (SWOG) trial 8794,[29] EORTC trial 22911,[30,31] and Arbeitsgemeinschaft Radiologische Onkologie (ARO) study 9602[32]; however, these studies shed light on only GU and rectal toxicities, as pelvic RT was not given to these patients. Complications were higher in men randomized to adjuvant RT in SWOG 8794 and included proctitis or rectal bleeding in 3.3% of the treatment group vs none of the men in the observation group. Urethral stricture and total urinary incontinence rates were also higher in the adjuvant RT arm compared with observation (17.8% vs 9.5% and 6.5% vs 2.8%, respectively). However, global assessment of quality of life became similar by 24 months after RT, and quality of life was increasingly superior in the adjuvant RT arm over the following 3 years. In EORTC 22911, grade 3 toxicity at 5 years was reported in 4.2% and 2.6% of men on the RT and observation arms, respectively. Although the risk of urinary incontinence with postoperative RT appears to be low, it is anticipated to have a negative impact on recovery of sexual function for previously potent men who have undergone a bilateral nerve-sparing RP. Lastly, external beam RT as primary treatment for localized PCa is associated with a low but significantly increased risk of secondary malignant neoplasms,[33,34] and postoperative RT is likely to be associated with similar risks. In the current era, postoperative RT may be associated with an improved toxicity profile, given the development of modern conformal therapy with or without image-guided techniques, as well as use of CT-based delineation of treatment targets, taking into account the operative and pathologic reports, and incorporating guidelines for contouring the planning target volume and selecting adequate margins. Because of a great variation in the definition of clinical target volumes for pelvic nodal RT,[35] RTOG has established a consensus atlas, which should be used by treating radiation oncologists to avoid excessive toxicities, while providing an adequate coverage for lymphatic targets at risk for harboring occult disease. Muller et al[36] recently reported their toxicity outcomes for 39 patients treated with pelvic IMRT for LN+ PCa. Among these patients, 18 men were treated after RP and PLND, to 45 Gy to 50.4 Gy. The remainder were treated definitively with IMRT with boost doses of 60 Gy to 70 Gy to radiographically evident LNs; all received combination treatment with ADT. Acute grade 3 or higher radiation-related toxicity occurred in two patients (urinary obstruction in one patient and ileus in the other). With a median follow-up of 70 months, fewer than 50% of patients reported mild late GU and GI toxicities, and none developed grade 3 or higher late toxicities.

### The Role of Imaging in Detecting and Directing Treatment for Patients With LN+ PCa

Despite the present decline in incidence of pN+ PCA due to the earlier detection of cancer with PSA screening, newer and better imaging technologies are likely to detect early involvement of LNs in an increasing number of patients. This will raise an important question of proper treatment for patients with small nodal bulk disease, as identified by newer imaging tools at the time of initial staging workup. Whether surgery or radiation or both, in conjunction with ADT, will be the primary treatment modalities will be a consideration for future studies. MRI appears to be better than CT for detection of pelvic LNs in GU malignancies, especially for LNs in the size range of 1 mm to 5 mm. Among 30 patients with prostate and bladder cancer who underwent CT and MRI for nodal staging, CT detected 189 pathologically involved nodes, compared with 271 nodes detected by MRI.[37] Lymphotropic nanoparticle-enhanced MRI (LNMRI), also known as magnetic resonance lymphography (MRL), is able to identify occult lymph node metastases in patients who are believed to be node-negative by conventional CT imaging staging studies. Ross et al[38] published a series of 26 patients after RP who were candidates for salvage RT and were believed to be node-negative. Of these 26 patients, 6 (23%) tested as LN+ by LNMRI. This rate was 72% in a more recent series by Meijer et al.[39] Positron emission tomography (PET)/CT with 11C-choline and 18F-choline tracers has already been proposed as valuable in the evaluation of PCA patients.[40-43] The accuracy of PET/CT in detecting LN metastases in patients with a PSA relapse has only been assessed in a few studies to date. De
Jong et al.[44] evaluated 22 patients with $^{11}$C-choline PET/CT after PSA relapse, and 5 of these patients showed increased uptake of choline in pelvic LNs, proven to be true positive by lymphadenectomy in all of these patients. In a different study, the same group reported that $^{11}$C-choline PET/CT imaging of LNs in patients with PCa had sensitivity of 80%, specificity of 96%, and accuracy of 93%.[45] The use of $^{18}$F-fluoroethylcholine (FEC)-PET/CT in RT planning has recently been described by Wurschmidt et al.[46] and presents a novel method of image-guided dose-escalation to the FEC-positive LNs. Among the 24 patients with FEC-positive disease, treated with RT for primary or recurrent PCa, with the median follow-up of 2.4 years, bFS was 83% in primary disease and 49% in recurrent disease. The median dose to the FEC-positive pelvic LNs was 66.6 Gy, with moderate (grade 2) late rectal and GU side effects seen in 15% of patients. This new imaging technology appears to enhance our ability to identify small pathologically involved LNs and guide the delivery of RT with curative doses over 60 Gy. Carefully designed studies with longer follow-up will reveal whether this approach can improve outcomes in this selected group of patients.FIGURE 3

| Treatment Algorithm Proposed by the Authors for the Multidisciplinary Management of Patients With Lymph Node–Positive Prostate Cancer. |

**Conclusion**

At the present time many clinicians still shy away from local therapies in patients with LN+ PCa. Guidelines do not offer much specific guidance, besides mentioning various treatment options, from observation, to systemic therapies, to combination therapies. Certainly outcomes in patients with disease spread to regional LNs are much worse than those in patients with localized PCa. At the same time, they are much better than those in patients with bony metastases. Because of different outcomes, we believe AJCC should re-evaluate grouping patients with LN+ disease in the same stage IV category as patients with M+ disease. The review of the literature suggests local therapies are associated with improvement in local control as well as PCSS and OS rates, although future randomized trials are needed to provide further guidance to patients and clinicians. The median survival for these patients may extend to many years, and some patients can live for more than a decade. As novel targeted agents and systemic treatments enter the armamentarium, patients with these advanced diseases will live longer, and local control will become ever more critical for their disease control and quality of life. Novel systemic therapy trials in combination with local therapies are needed to improve the outcomes for these patients, and in the absence of novel targeted agents, we advocate for a multimodality treatment algorithm, such as the one outlined in Figure 3.

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