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Postoperative Radiation Therapy for Metastatic Cervical Adenopathy

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The management of cancers of the head and neck focuses on primary site and regional (neck) disease control. Many patients are treated with surgery as the principal mode of treatment, and surgery often includes an elective or therapeutic neck dissection. Risk factors assessed for recurrence subsequent to neck dissection include nodal size, number, levels, and the presence of extranodal spread. Adjuvant radiation therapy (with or without chemotherapy) is offered to patients deemed at sufficient risk of recurrence based on assessment of these factors. However, randomized trials have not been performed to test the need and/or benefit of adjuvant postoperative radiation. The necessity of adjuvant radiation has been based on decades of clinical observations, retrospective studies, and indirect randomized trials. The case for postoperative radiation for patients with adverse features in the neck, and recommendations are made in the accompanying article.
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General Principles of Postoperative Radiation

More than half a century ago surgery and radiation were the 2 modalities of therapy available for the treatment of head and neck cancers. Both surgeons and radiation oncologists recognized that while their respective therapies often helped rid patients of their disease, these therapies had limitations. Extensive, aggressive surgeries often would have negative impact on patients' quality of life without offering additional therapeutic benefit. Radiation therapy had limitations in dose due to potential complications, and was less effective in managing advanced disease. These clinicians had the foresight to recognize that their therapies were not competitive, but rather complementary, beginning the era of combining radiation and surgery.

Initially this concept was rudimentary and complicated by a lack of data to guide how best to sequence these 2 therapies. Physicians recognized advantages and disadvantages to both radiation before or after surgery. Favoring postoperative radiation were (1) the ability for the surgeons to operate in nonviolated tissues, (2) the ability to give more radiation dose (since it was believed that preoperative radiation should be limited to no more than 50 Gy), and (3) to obtain the optimal understanding of the pathologic findings, both for the surgeon to best understand margin checks intraoperatively and the radiation oncologist to best tailor the postoperative therapy. At the time, the majority of patients who underwent combined surgery and radiation were preselected based on the clinical examination findings. Now, pathologic findings drive the decision making process, in regard to deciding if adjuvant therapy is warranted, determining the specifics of the adjuvant treatment, such as radiation dose and volume, and the need for concurrent systemic therapy.

To better understand whether preoperative or postoperative radiation therapy resulted in better outcomes, comparative trials were conducted. A small French trial conducted in the late 1960s randomized patients with advanced hypopharynx cancer to 55 Gy delivered either preoperatively or postoperatively.[1] There was a statistically significant better survival in patients treated postoperatively. Subsequently, the Radiation Therapy Oncology Group (RTOG) conducted a randomized trial, RTOG 73-03 (the "73" signifying the year of initiation, 1973).[2] Patients with previously untreated squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx who were considered to have operable T3 or T4 primary tumors were eligible and were randomized to preoperative or postoperative radiation. The treatment volumes were the same in both arms, with a goal of 4 weeks between surgery and radiation. Patients in both arms received 50 Gy at 1.8-2 Gy per fraction, with those patients in the postoperative arm receiving a 10 Gy boost to the primary tumor bed. The design was complicated

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by allowing patients with oral cavity and oropharynx cancers to potentially be randomized to a third, definitive radiation arm.

Two-hundred seventy seven patients were analyzed (136 in the preoperative arm and 141 in the postoperative arm). The final report, with 10-year median follow-up, revealed that patients treated with postoperative radiation had improved local regional control, but not improved survival compared to patients treated preoperatively. Complications and distant recurrence rates were similar between the 2 arms of the study. The finding of a significant improvement in local-regional control led to the adoption of postoperative radiation being the adjuvant treatment of choice with surgery for patients with advanced head and neck cancers.

Timing

The timing of postoperative radiation was based on the expectation that the surgical wound would be healed at the time of radiation. Fletcher[3] believed that most patients would be ready for radiation within 3 weeks of surgery, though 4 weeks was a common recommendation, was the time frame incorporated into RTOG 73-03,[2] and was typically the minimum interval used in subsequent postoperative radiation trials.

The maximal time interval is controversial. Based on a report by Vikram et al.,[4] an interval of >6 weeks between surgery and the start of radiation was deemed deleterious due to the observation that patients who started their radiation after 6 weeks experienced more neck recurrences. The authors postulated that the extent of surgery could be contributory, and those patients who had more radical procedures had more disease so were more prone to delay, but their analysis refuted this hypothesis. A subsequent publication from the same institution[5] reported that the higher rate of failure in patients whose radiation started more than 6 weeks from surgery was only observed in patients who received <60 Gy. The authors concluded that poorer outcome was related to dose and not timing.

An analysis from the University of Florida[6] described their patients starting radiation 1-10 weeks from surgery, and could not demonstrate worse outcomes in patients with increasing surgery-radiation intervals, specifically for the ≥6 week interval, but also for other weekly intervals. In a more recent work focused on patients with oral cavity cancer, Langendijk et al.[7] analyzed the time between surgery and radiation and outcomes (local regional control, disease-free survival, and overall survival). Sixty percent of 217 patients did not start their radiation within 6 weeks following surgery, yet similar to other reports, the authors found no association with this time interval and outcomes. Despite these studies, the 6 week interval is ingrained into the culture of most radiation oncology departments and is often employed.

Others have focused not on the surgery to start of radiation time, but rather the surgery to end of radiation time, or overall treatment "package." A randomized trial compared 63 Gy delivered in 5 weeks vs 7 weeks for patients with high-risk head and neck cancer treated with surgery and postoperative radiation.[8] While there was only a trend to improved outcomes in patients treated with the accelerated 5-week course, a secondary analysis revealed that the patients who did worse were those who received 7 weeks of radiation and did not start their treatment within 6 weeks of surgery. Those whose overall treatment time was greater than 13 weeks had the worst outcomes. Parsons et al.[9] and Rosenthal et al.[10] also observed that a prolonged overall treatment package was detrimental to outcomes. A final report of the MD Anderson postoperative dose seeking trial[11] reported that an overall package time of >85 days resulted in poorer outcomes. However, as longer packages were often associated with higher doses, it is important to recognize that if the time interval between surgery and the start of radiation is prolonged, simply compensating by adding more dose (over more days) is not effective.

Radiation Dose

The appropriate dose for postoperative radiation has largely been empirically driven. Fletcher and colleagues had established that 50 Gy was adequate for elective nodal coverage in the N0 neck, with disease control rates in the neck of >90%.[12] It had also been established that gross disease required a minimum of 60 Gy, and more often higher doses to obtain disease control. At MD Anderson, concerns for tumor repopulation and hypoxia led to the belief that postoperatively more than 50 Gy is required, and 60 Gy would provide additional benefit in disease control, while maintaining acceptable rates of complications. In switching from preoperative to postoperative radiation, the head and neck radiation oncologists at Memorial Sloan Kettering also used doses of 50–60 Gy.[4] However, many believed that doses >60 Gy were indicated if there were adverse pathologic features. For example, Cachin and Eschwege at Institute Gustave Roussy, were among the first to recognize the negative prognosis associated with extranodal extension (ENE).[13] They recommended 50 Gy for the node positive neck without ENE, but an additional 15-25 Gy boost to a smaller volume that harbored nodes with ENE.

Recognizing that the dose required to prevent recurrences in the postoperative setting was poorly established, Marcus and colleagues at The University of Florida performed a retrospective analysis of 71 patients.[14] Patients received doses ranging from <40 Gy to >65 Gy, typically delivered at 1.7-1.8 Gy per day. The principal findings were that there were fewer recurrences in patients who received ≥60 Gy, and doses >65 Gy (even as high as 70 Gy) may be required for oral cavity and oropharyngeal tumors.

To better determine the optimal dose of postoperative radiation, Peters et al. at MD Anderson conducted a prospective randomized trial.[15] Patients were randomized to 1 of 3 doses, 54 Gy, 63 Gy, and 68 Gy. All patients were treated at 1.8 Gy per fraction. After an interim analysis, the lowest dose was increased to 57.6 Gy. The randomization was dependent on establishing the degree of risk of recurrence

(based on accepted risk factors at the time of the study) at the primary site and neck. Randomized doses were assigned separately to the primary site and neck. The operated site and both sides of the neck were treated to 54 Gy, and the final doses were boosts to the defined sites of risk. The study results demonstrated no obvious dose response beyond 57.6 Gy with the exception of patients with ENE, who had fewer recurrences if treated to at least 63 Gy. Doses above 63 Gy appeared associated with a greater incidence of complications. Thus the authors recommended 57.6 Gy to the entire operative bed with a boost to 63 Gy to sites of increased risk, particularly ENE. This study was not only valuable in defining dose, but also in defining differing risk categories for targets of intensification of treatment.

However, the studies to date have not made closure on the appropriate total dose. In subsequent multi-institutional trials focusing on high-risk patients, the RTOG has allowed a range of dose, with a minimum of 60 Gy, but allowing for 66 Gy,[16] while the European Organization for Research and Treatment of Cancer (EORTC) chose 66 Gy in its seminal postoperative trial.[17]

In addition to the question of total dose, there has also been a question of dose per fraction. The earliest experiences favored 2 Gy per fraction, or 10 Gy/week. However, the concerns for complications led to either allowing a break of several weeks, which has been determined to be detrimental and to be avoided, or to lowering the dose per fraction to 1.7-1.8 Gy.[14] There have not been studies specific to fraction dose. Rather the eventual recognition of the importance of overall time led to the return of 2 Gy fraction size.

It is important to also remember that our concept of radiation dose continues to change. The doses recommended in the 1970s-1980s were typically delivered with Cobalt60 and prescribed to the central axis or isocenter of very large fields. Using IMRT or other conformal approaches with dose specified to a large target volume compared to a point likely has resulted in a subtle form of unappreciated dose escalation.

The Neck

Most patients with head and neck cancer who are treated with surgery have squamous cell carcinomas of the oral cavity, oro- and hypopharynx and larynx. All these sites have drainage to the lymphatics of the neck, and many patients (particularly those with advanced primary tumors) develop neck metastases. The incidence of lymph node metastases from the common primary sites was detailed by Lindberg and ranged from 30.5% for floor of mouth cancers to 75% for cancers of the hypopharynx.[18] Most patients presenting with clinical adenopathy had therapeutic neck dissections. The classical approach was a radical neck dissection, but surgeons in the 1960s and 1970s began to explore a more tailored dissection, or "functional" neck dissection. Additionally, the realization that recurrence rates were high with surgery alone and that radiation could help manage the residual microscopic disease led to a move away from radical resections.

A precise understanding of the risk of recurrence following a therapeutic neck dissection is challenging, as the literature is inconsistent. Many of the papers on surgical outcomes in the treatment of head and neck cancer focused on outcomes related to the primary site and outcomes regarding the neck were either considered secondarily or not at all. Those that did have some focus on the neck further confounded our understanding as the endpoints considered were varied. The endpoints from that era included: crude survival rates, recurrence in the operated neck, recurrence in the contralateral unoperated neck, and control above the clavicles. The most informative endpoint for understanding management of the neck was the recurrence rate on the operated neck. Articles from the Mayo Clinic and Memorial-Sloan Kettering Cancer Center from the 1960s are some of the earliest reported experiences; Beahrs and Barber[19] reported a recurrence rate of 32% in patients with a mix of primary tumors who had radical neck dissections and positive nodes. Strong et al. reported an overall recurrence rate in the neck of 33%, but a rate of 50% in those with positive nodes.[20] Two decades later, papers focusing on the outcomes of functional rather than radical neck dissections revealed similar recurrence rates in node positive operated necks.[21,22]

As strong advocates of adding radiation to surgery, Fletcher and colleagues compared results of surgery only to combined therapy.[3] In addition to recurrences in the ipsilateral neck their data added 2 points of information: (1) frequency of recurrences in the nonoperated contralateral neck, and (2) a more robust analysis of recurrence by stage. Data from Barkley et al. revealed that in patients treated with surgery alone there was a recurrence rate of 21%, and a 28% rate of recurrence in the nonoperated clinically negative neck.[23]

The work of Barkley et al.[23] also described a staging system for nodal disease that had been used since the 1950s, and ultimately was very similar to that incorporated into the first iteration of the American Joint Commission on Cancer staging system. Sequentially the system defined increasing risk of poorer outcomes based on nodal size (< or >3 cm), multiplicity, fixation, and bilaterality. During that era imaging was crude, and staging as well as treatment decisions were largely based on clinical grounds. The report of Beahrs and Barber[19] suggested a near 90% correlation between clinical assessment and pathologic findings (with regards to whether the neck harbored disease), allowing clinicians a comfort level with the accuracy of clinical staging. This comfort with the relative accuracy of clinical staging, and the practice of selecting patients at presentation for combined therapy, often with preoperative rather than postoperative therapy delayed incorporation of pathologic staging into treatment decisions.

Many of the pathologic features studied were also inconsistently shown to be of prognostic value. These included differentiation, inflammatory response, and sinus histiocytosis.[24] The one pathologic feature for which there appeared to be uniform acceptance as being an excellent predictor of outcome was ENE. Cachin and Eschwege[13] demonstrated in the early 1970s that ENE (described as capsular rupture) was significantly predictive of outcome. They divided patients into 3 prognostic groups: (1) node negative (2) node positive without ENE and (3) node positive with ENE. Three-year

survival rates were 65%, 33%, and 16% respectively for these 3 groups. Noone et al.[25] and Shah et al.[26] described the negative impact of ENE on patients with oral cavity cancers, and Bennett et al.[27] and Sessions[28] similarly described the finding of ENE portending poorer survival in patients with cancers of the larynx and hypopharynx.

However, there was a general belief that ENE was highly correlated with fixation of nodes, nodal number, and tumor size. Fixation in particular was thought to be caused by tumor breaking through the nodal capsule and invading adjacent soft tissue. Snow et al.[29] performed a histologic analysis to better assess the relationship of ENE with these clinical correlates. ENE was found in 70% of cases with fixation, and 33% in the absence of fixation. There was a greater probability of ENE with multiple nodes (64%) compared to a single node (40%). Finally, there was an increasing rate of ENE with increasing size, as nodes > 3 cm had a near 74% rate of ENE. However, and perhaps more importantly, even small nodes had modest rates of ENE ranging from 23% to 53% with sizes >0 cm to <3 cm. A similar observation was reported by Johnson et al.,[24] who found an incidence of ENE in 65% of nodes <3 cm. Both reports again emphasized the negative impact of ENE, and Johnson et al. further demonstrated that ENE was more relevant than differentiation or multiplicity of nodal disease. They advocated that ENE should be incorporated into the staging, but it took decades for ENE to finally be a component of nodal staging.

In the MD Anderson dose seeking trial[15] the risk of recurrence in the neck was determined based on 5 adverse features described in the literature: nodal number, number of nodal groups, nodal size, ENE, and direct invasion. The results reported in crude recurrence rates above the clavicle demonstrated a trend to worse control when multiple nodes were present (25% vs 12%, $P = 0.08$) and when ENE was present (26% vs 13%, $P = 0.04$). The analysis further revealed that ENE overwhelmed the other potential prognostic factors; these factors were only relevant when ENE was not present, and then a worse prognosis was only observed if multiple adverse features were present. Also, while overall no dose response was observed, when ENE was present, the 2-year actuarial control rates were 52%, 74%, and 72% for 57.6 Gy, 63 Gy, and 68.4 Gy, respectively ($P = 0.03$).

In a separate analysis investigators evaluated RTOG 85-03,[30] an Intergroup phase III trial testing adjuvant chemotherapy (sequentially between surgery and postoperative radiation). Similar to the trial of Peters et al., they too found that ENE and/or multiple nodes increased the risk of recurrence. This analysis combined with the results and analysis of RTOG 88-24, a phase II trial testing the addition of cisplatin to radiation led to the conducting of 1 of 2 seminal trials in postoperative radiation.

RTOG 95-01 was a phase III randomized trial comparing postoperative radiation alone with radiation combined with 3 cycles of cisplatin (100 mg/m^2 on days 1, 22, and 43).[16] Patients with squamous cell carcinoma of the oral cavity, oro- or hypopharynx, or larynx who underwent surgical resection of their disease were potentially eligible. Based on previous studies, this study targeted patients at "high-risk" for recurrence and with regards to the neck included patients with either multiple nodes or ENE. Ninety-four percent of the 459 patients enrolled had N2-3 disease. The primary endpoint was the 2-year local-regional control rate, and was 72% in the control arm compared to 82% in the experimental arm ($P = 0.04$).

The EORTC conducted a very similar trial.[17] The principle differences from RTOG 9501 were the endpoint (3-year progression free survival) and eligibility. Patients with pathologic stage III-IV disease were eligible; thus any patient with nodal category N2 or greater would qualify as well as those with smaller volume nodal disease with ENE. However, because of broader eligibility based on primary tumor features, only 57% of patients on the EORTC trial had N2-3 disease. The EORTC trial was positive not only for its primary endpoint, but also for improvement with chemotherapy on local regional control and overall survival.

The 2 groups pooled their data,[31] and focused on the 2 "high-risk" features in common for both trials: ENE and positive margins. The distribution of patients with ENE was 57% and 53% for the EORTC and RTOG cohorts, respectively. They found that the superiority of concurrent therapy over radiation alone (regardless of endpoint) was linked to the presence of one or both these risk features. They also could not show a benefit to cisplatin plus radiation in patients with 2 or more nodes as the only risk factor. These 2 randomized trials and their interpretations have led to recommendations for concurrent cisplatin and postoperative radiation in patients with ENE found at neck dissection.

While the interpretations of these trials and in particular the conclusion that patients with ENE benefit from the addition of cisplatin to radiation is generally accepted, it is not universally accepted.[32] In particular, with the recognition that patients with HPV-associated cancers have dramatically superior outcomes compared to patients with oropharyngeal cancer that is not HPV-associated, the question of the significance of ENE has resurfaced. Sinha et al. describe their novel grading system for ENE in HPV-positive tumors.[33] They exclude nodes with capsular thickening, and then divide ENE by < or >1-mm-extension beyond the capsule and a third group with soft tissue deposits and no recognizable nodal architecture. In one of their analyses[33] of 133 patients with neck disease at operation, the ultimate regional control irrespective of adjuvant therapy was 97%. They concluded that routinely reported ENE should not be an indication for adjuvant chemotherapy.

In a subsequent retrospective multi-institutional trial[34] of over 700 patients with HPV-associated disease discovered in the operated neck, ENE was not a statistically significant predictor of outcome, while ≥5 nodes was a negative prognosticator. The recent 8th edition[35] of the American Joint Commission on Cancer staging now includes a separate staging for oropharyngeal HPV-associated disease, and based on these works further includes a pathologic nodal staging that is determined by the number of nodes and not ENE. These experiences also led The Eastern Cooperative Oncology Group (ECOG) to consider ENE <1 mm as an intermediate rather than high-risk feature in their recent trial assessing transoral surgery for HPV-associated cancer. Intermediate-risk patients received

adjuvant radiation while high-risk patients received concurrent chemoradiation postoperatively.

The recent interest in data-mining of large databases led Trifiletti et al. to analyze postoperative chemoradiotherapy utilization and outcomes of head and neck cancer patients captured in the National Cancer Database.[36] Analyzing over 10,000 patients with negative surgical margins and no extracapsular extension, the authors noted that 47% of patients received chemotherapy with radiation. Increasing use of chemotherapy was observed with increasing nodal number, as 75% of patients with >4 nodes received chemotherapy. There was a small survival benefit (Hazard ratio = 0.9) for those receiving chemotherapy. Regardless of whether patients received chemotherapy, nodal number was associated with survival, with an approximate 10% and 20% reduction in absolute 3- and 5-year survival rates for patients with 2-4 nodes and >4 nodes, respectively compared to patients with 1 node positive.

The focus above has been principally on high-risk features predicting neck recurrence. The role of radiation is more controversial in patients with lower risk features, particularly pN1 disease without ECE. This controversy further extends to patients with low risk of primary recurrence, that is patients with pT1-2 disease without adverse features predicting primary recurrence. Early advocates of postoperative radiation, such as those at MD Anderson, recognized that patients treated with surgery alone who presented with a clinical solitary node had an ipsilateral recurrence rate of 10%[23]; however the recurrence rate in the contralateral neck was 18%. The recurrence rate in either neck approached 0% when postoperative radiation was added. The authors concluded that combined modality was superior, but did state that radical neck dissection is effective for a single first level node provided the cancer has not broken through the capsule.

Million and Cassisi[37] advocated postoperative radiation if the risk of recurrence was >20%. They concluded for the data available at the time that in the absence of ENE, postoperative radiation was not recommended for pN1 disease. Two recent database analyses, one from the National Cancer Database,[38] and one from data from the Surveillance, Epidemiology, and End Results database,[39] mined the respective databases for patients with T1-2N1 oral cavity and oropharynx cancer to address this question. Both suggested a survival benefit in patients receiving radiation, particularly those with T2 disease.

Conclusions

Over half a century ago clinicians observed that patients with squamous cell cancer metastatic to the neck had frequent recurrences in the neck following radical neck dissections, and advocated combined modality therapy. A specific phase III trial comparing surgery alone vs postoperative radiation has not been conducted. There is a large body of retrospective data and a case control trial[40] demonstrating a benefit to postoperative radiation. In addition, there have been sequential randomized trials demonstrating preoperative radiation followed by surgery is superior to surgery alone,[39] postoperative radiation is superior to preoperative radiation,[1,2] and for "high-risk" patients (with differing definitions of high-risk), postoperative combined cisplatin and radiation is superior to postoperative radiation alone.[16,17] Many questions remain, including: (1) how to further improve results for "high-risk" patients beyond Harrison LB, Strong EW that achieved with cisplatin radiation, (2) what is the optimal adjuvant approach for patients with HPV-associated neck disease, and (3) do patients with small volume non-HPV- associated disease need adjuvant treatment?

To further improve outcomes for high-risk patients with non-HPV associated disease, the RTOG has and continues to test taxane and cetuximab-based radiation therapy.[41] EA3132 is a postoperative trial sponsored by ECOG that rather than try to identify patients who would benefit from cisplatin added to radiation by classic clinical-pathologic findings is testing whether patients with and without p53 associated tumors would benefit from chemoradiation. For patients with HPV-associated oropharyngeal cancer ECOG has completed enrollment in a large phase II trial (E3311) studying the efficacy of transoral surgery and neck dissection. The Mayo Clinic group has also completed accrual of patients treated with transoral surgery for HPV-associated disease, testing lower doses of adjuvant radiation with taxanes. MacComb and Fletcher[42] are often credited with being the first advocates of combined modality therapy. More than 60 years later, questions of which patients benefit most, what is the optimal radiation dose and more recently, whether to add systemic therapies and which systemic agents perform best, remain.

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