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FRACTIONATION AND CHANGES IN PATIENT CARE

COVID-19—An Opportunity for Optimizing Surveillance Protocols During and Beyond the Pandemic: HPV-Associated Oropharyngeal Cancer as an Example of Response-Based Local Surveillance

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The emergence of the novel coronavirus dubbed severe acute respiratory syndrome coronavirus 2, or more commonly referred to as COVID-19, heralded the arrival of significant global disruptions to the provision of routine cancer care in early 2020.[1] In response, the radiation oncology community rallied to produce international consensus guidelines across the breadth of oncology settings to assuage the stress on individual health care providers, providing direction on treatment prioritization during periods of significantly restricted health care resources. As many health care systems emerge from the initial wave of acute COVID-19 infections, our specialty needs to carefully consider how we will maintain the safety of our frontline health care workers in the setting of endemic COVID-19 prevalence and reduce exposure where safe and feasible.

One strategy rapidly implemented during the acute phase of the pandemic was the use of telehealth consultations, allowing clinicians to remotely assess the progress and symptoms of their patients, while simultaneously removing the opportunity to directly examine the patient, an integral component of the physician—patient consultation. Although this strategy was necessary during the short-term duress of the pandemic, it also focusses the spotlight on the broader issue of the effectiveness of our current surveillance strategies. Could COVID-19 provide the impetus for our specialty to question what are largely generic surveillance strategies and venture into evidence-based approaches in which follow-up protocols are based on individual biological risk and treatment response? Although this opinion piece will focus on the necessity of local surveillance in human papillomavirus—associated oropharyngeal cancer (HPV-OPC), a distinct cohort of patients with favorable-prognosis head and neck cancer (HNC), it is hoped this may stimulate a wider discussion about the current varied surveillance strategies across our specialty.

In contemporary HNC practice, the increasing incidence of HPV-OPC has resulted in these patients now forming a

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considerable proportion of our follow-up clinics. Routine examination of patients with HPV-OPC generally includes both direct oropharyngeal palpation and visualization with a flexible nasoendoscope, both procedures that can potentially result in aerosolization, placing the treating physician at increased risk of contact with respiratory airborne infections, including COVID-19. This increased risk is, however, almost entirely mediated during the evaluation of patients for local failure, an exceedingly rare event in HPV-OPC, dwarfed by the risk of both regional and distant recurrence. This raises the question of the necessity of placing our workforce at risk while performing low-yield procedures during a time of potentially low but ongoing community COVID-19 prevalence.

Over the last 20 years, considerable effort has been undertaken to define the role of posttreatment fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (FDG-PET/CT) metabolic response to stratify patients after (chemo)radiation therapy (CRT). In line with National Comprehensive Cancer Network guidelines, most consider an FDG-PET/CT between 3 to 6 months after CRT as standard.[2] Where a complete metabolic response (CMR) has been achieved after treatment, there is very little data to support further imaging surveillance in asymptomatic patients. In those with an equivocal scan, a "second-look" PET/CT can be invaluable, with many patients subsequently converting to a CMR, obviating the need for an unnecessary neck dissection or examination under anesthesia.[3-5] With the increasing incidence of HPV-OPC, a substantial proportion of the posttreatment FDG-PET/CT literature has either focused on or included significant proportions of patients with this disease. In HPV-OPC, where the neck response can lag behind that of the primary site and the predominant pattern of recurrence is distant or regional failure,[5-8] it is not surprising that much of the published research on FDG-PET/CT has focused on the assessment of the neck. However, in the current COVID-19 climate, further scrutiny of the published data may generate an opportunity to propose a safe, reduced-intensity recommendation for local surveillance after a primary CMR in patients with HPV-OPC.

Table 1 Studies reporting long-term local control outcomes after negative posttreatment positron emission tomography–computed tomography outcomes stratified by human papillomavirus status

First author	No.*	Timing post-CRT, wk	Median follow-up, y	Local NPV	Any LF	Detection of LR	Median time to LF	CMR criteria
Urban[9]	556	Median 13.7	2.6	100%	NA	NA	NA	Any focal moderate or intense uptake (RD); mild nonfocal or no uptake (CMR)
Ng[8]	291	4-12	4.5	-	3/291 (1%)	1 isolated LF detected on imaging, 1 LRF and 1 LRDF failure detected clinically	NR	Hopkins criteria
Vainshtein[5]	67	≥12	3.7	98%	2/67 (3%)	1 LF detected on serial PET/CT with previous CMR at 3-mo PET/CT	9.4 mo	SUV <6.5 for primary and <2.8 for LN
Chan[7]	67	Median 12.5	2.2	NR	2/67 (3%)	NR	NR	SUV <2 or <2.5
Sjövall[6]	59	12 ± 16-18 second look	5.2	NR	1/59 (1.7%)	NR	NR	No avidity above background or diffuse uptake in absence of corresponding structure abnormality
Moeller[12]	61†	8	1.8	98%	NR	NR	NR	Reported threshold values for SUV; <6.5 for primary and <2.8 for LN

Abbreviations: CRT = chemoradiation therapy; CMR = complete metabolic response; LF = local failure; LRDF = local, regional, and distant failure; LRF = locoregional failure; LN = lymph node; NPV = negative predictive value; NR = not recorded; RD = residual disease; SUV = standardized uptake value.

* Indicates number of patients in the study with a negative posttreatment fluorodeoxyglucose-positron emission tomography/computed tomography at the primary site.

† Post hoc low-risk group consisting of human papillomavirus–positive/oropharyngeal nonsmokers.

Selected studies that have either focused on, stratified by, or reported FDG-PET/CT outcomes for HPV-OPC are summarized in Table 1. These selected studies have included details from which the response and subsequent outcomes can be determined for the primary site. In these series, the reported rate of local recurrence after a CMR at the primary site ranges from 0% to 3% (Table 1). In the largest of those series, Urban et al from Vancouver reported a primary negative predictive value of 100%[9]; in other words, in their series of 648 oropharyngeal patients (556 HPV+ and 92 HPV−), there were no reported failures at the primary site in the HPV-OPC group after a CMR, with a median follow-up of 31.5 months. In that series, the predictive value was high irrespective of HPV status, a finding that has also been seen in other series.[10]

In the exclusive HPV-OPC series reported by Ng et al from the MD Anderson Cancer Center, only 3 primary recurrences were reported in the 291 patients who had had a CMR after CRT. Of those primary failures, only 2 patients presented with isolated local or locoregional disease, and the third had concomitant local, regional, and distant failure. Distinguishing those with isolated local or locoregional failures from those with concomitant distant failure has not always been reported in other series and remains a pertinent point, considering the utility of local surveillance primarily hinges on detecting early salvageable recurrences. Although the rates of primary recurrences did not vary significantly across the included studies, it was also noteworthy that the larger and most recent studies reported by Urban et al and Ng et al also reported the lowest rates of subsequent failure, suggesting the possibility that increased experience or volume may improve the diagnostic performance of posttreatment FDG-PET/CT.

Varying among the studies presented in Table 1 is the criteria used for classifying a CMR after CRT. Although there is no universally agreed upon system, a number of different systems have been proposed and compared and have shown similar diagnostic performance.[11] Where there are no universally agreed upon definitions, this unfortunately does raise the possibility of variations in the quality of posttreatment reporting. Although PET/CT was initially the domain of large academic centers, the more widespread use within the community should mandate minimum reporting standards and consensus guidelines to ensure the diagnostic accuracy of these scans are maintained.

Although the previous FDG-PET/CT literature primarily focused on assessment of the neck, now is the time to revisit these studies with respect to the low rates of primary failure. The data suggest that clinical evaluation of the primary site could be almost entirely omitted from routine clinical surveillance in these patients without a negative impact on the patient, while improving personal safety for HNC clinicians. As a secondary gain, optimizing surveillance protocols and procedures may provide an opportunity to reduce costs for an already burdened health system. In an Australian study, Shah et al showed that reducing the requency of surveillance visits from 3 to 6 months in a population of general patients with HNC who had achieved a posttreatment PET/CT CMR allowed for a substantial reduction in costs to the health system, without detriment to patient outcomes.[12]

Although we are suggesting that local surveillance can be reduced, we are not recommending against regular face-to-face follow-up altogether, but rather suggest there is scope to finesse routine follow-up both now and beyond COVID-19 in selected patients. Examining patients for recurrent disease is but one aspect of the follow-up consultation. Face-to-face consultations also allow for managing late treatment side effects, provide an opportunity for psychological reassurance, and facilitate screening for second primary malignancies (a much less frequent occurrence in patients with HPV-OPC). Physically examining a patient also allows the radiation oncologist and our trainees to most accurately understand the functional impact of our treatments on the surrounding normal tissues. However, we think the "standard" 3- to 4-month routine surveillance is inappropriate given the low rate of failure in HPV-OPC. We would suggest that after a posttreatment CMR, patients with HPV-OPC could be safely reviewed biannually, limiting direct local examination to those patients with new clinical symptoms or signs. Although we believe the data justify this approach, practitioners should keep in mind that the long-term accuracy of PET/CT will need to be re-evaluated where de-escalation approaches have been used; the current data are generated from patients treated with generally full-intensity treatment.[13]

As we transition into the next phase of the COVID-19 pandemic, we believe that this is a pertinent time to critically reflect on our current routine surveillance policies/practices. Where safe and evidence based, we should be considering how to reduce high-risk activities, such as local surveillance in select patients with HNC, and how to reduce general patient traffic through our workplaces.

Future strategies that may offer promise in refining surveillance strategies based on individual risk include tumor profiling and post-treatment biomarkers and liquid biopsies. With many ongoing uncertainties about exactly how COVID-19 will shape our workflow in the immediate future, this becomes a pertinent time to consider optimizing our current policies. Assuming an ongoing community COVID-19 transmission for the foreseeable future without a readily available vaccine, and with uncertainties about reinfection, when will it be safe for us to return to our previous practices? Perhaps more importantly, *should* we revert back to our old practices? Although COVID-19 has been a challenging time for our community, it provides a well overdue cue for a rationalization of our follow-up policies, providing an opportunity for us to generate evidence-based surveillance protocols based on individualized risk and tailored to treatment response.

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