Impact of primary tumor volume on local control after definitive radiotherapy for head and neck cancer

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ABSTRACT: *Background.* The impact of primary tumor volume (pTV) on local control after definitive radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC) is unclear.

Methods. Pertinent literature was reviewed to address the impact of pTV on local control after definitive RT for HNSCC.

Results. Reproducibility of pTV calculations is probably influenced by interobserver variability and may be reduced by relying on experienced observers. The impact of pTV on local control after definitive RT is probably influenced by primary site. A relatively limited impact of pTV on local control after RT for oropharyngeal squamous cell carcinomas (SCCs) might be attributable to human papillomavirus (HPV) positivity.

Conclusion. pTV may be a useful parameter to select patients for treatment with definitive RT, particularly for those with laryngeal SCCs. Patients with high-volume primary cancers, in which the probability of local control with a functional larynx is low, are likely better treated with surgery.
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KEY WORDS: radiotherapy, head and neck cancer, carcinoma, local control, primary tumor volume

INTRODUCTION

The likelihood of local control after definitive radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC) depends on the radiosensitivity of the tumor and extent of disease. Radiosensitivity varies with primary site as well as other factors, such as high-risk human papillomavirus (HR-HPV) positivity and smoking history.[1,2] In general, squamous cell carcinomas (SCCs) of the tonsillar fossa and base of tongue have a higher likelihood of cervical lymph node metastases and are more radiosensitive than oral cavity SCCs.[3,4] To obtain an acceptable local control rate for T1 to T2 oral tongue SCCs treated with definitive RT, brachytherapy is used. It is unclear if the dose escalation inherent in the inhomogeneity of brachytherapy, the more accurate delivery of the radiation via implants compared to external radiation of a potentially moving target, or the decreased overall treatment time is the key to success. In order to obtain an acceptable local control rate for T1 to T2 oral tongue SCCs treated with definitive RT, it is necessary to compress the overall treatment time by using brachytherapy to deliver most of the RT dose, whereas this is unnecessary for base of tongue SCCs.[4,5] T1 to T2 anterior tonsillar pillar SCCs have a 70% local control rate after definitive RT, whereas T1 to T2 tonsillar fossa SCCs have local control rates exceeding 90%.[3]

Primary tumor extent is stratified into a T-classification based on parameters, such as maximum diameter, extension to adjacent sites, vocal cord fixation, and/or likelihood of complete resectability. Tumor volume is another parameter that reflects extent of disease and, depending on the radiosensitivity of the tumor, may predict the likelihood of control after definitive RT.[6–9] Primary tumor volume (pTV) may vary significantly with primary site, which may be related to the point at which symptoms are produced and the diagnosis established. For series of patients treated with a particular modality, such as RT, the availability of other appropriate treatment options, such as surgery for advanced laryngeal cancer, may influence the range of pTVs treated with RT.[10,11] Patients with high volume laryngeal cancers are more likely to have cartilage destruction and a poor outcome after definitive chemoradiotherapy (CRT) and are, thus, usually treated with a total laryngectomy.[12] It was not possible to

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accurately measure tumor volume before the availability of computed tomography (CT) and magnetic resonance imaging (MRI). However, over the last 2 decades, a number of authors have investigated the impact of pTV on local control after definitive RT. Following is a review of the pertinent literature.

Measuring primary tumor volume

In order to calculate pTV, the primary tumor is manually delineated with a mouse on serial CT or MRI slices. This allows the software to automatically calculate the areas of the lesion and, from the thickness of the slice, the volume of the tumor per slice and, finally, the sum of the volumes of all the slices.[13] The majority of the data pertaining to the impact of pTV on outcome after definitive RT have used diagnostic contrast-enhanced CT as opposed to treatment planning CTs or MRIs. Some have pointed out that MRIs are more accurate for measuring tumor volume than using the CT images for tumors of the oral cavity and oropharynx,[14] if the contrast between the tumor and the surrounding normal tissue is insufficient on the CT images, if artifacts obscure the tumor on the CT images, or if the tumor is very small.[15]

An issue central to the prognostic value of pTV is reproducibility. Hermans et al[16] reported on a study evaluating intraobserver and interobserver variability using pretreatment CT to calculate pTV for 13 patients with laryngeal tumors. Five observers calculated the pTV in 4 different sessions. Significant variability was detected and was related to both observer ($p < .0001$) and session ($p < .01$). Interobserver variability was the most important component and accounted for 89.3% of total variability. The authors stated that it would be ideal for one experienced observer to calculate pTVs. In agreement with these data, Gordon et al,[17] using an interactive computer program that enabled the extraction of tumor volumes from 3D MRI data in patients with pharyngeal carcinoma, determined the measurement error and percentage measurement error (intraobserver variability). The mean and median percentage measurement errors, respectively, were 13% and 12% for primary tumors, which had no statistical significance.

In contrast, Mukherji et al[18] reported excellent interobserver reproducibility for 4 neuroradiologists and 4 experienced radiation oncologists from different institutions who were asked to calculate the pTV on pretreatment CTs for 20 patients with supraglottic carcinomas. Been et al[19] reported on 70 patients with oropharyngeal SCCs in which the pTVs were calculated on pretreatment CTs by 2 observers and found high interobserver correlation.

It is likely that there is a variable degree of reproducibility when calculating pTVs and that this is mostly because of interobserver variability. Reproducibility is likely improved by using a small number of experienced observers and limiting pTV determinations to 1 type of imaging, such as pretreatment diagnostic CT, as opposed to MRI or treatment planning CT. Parenthetically, the author's impression is that treatment planning CTs tend to overestimate pTVs compared with diagnostic CTs.

In an attempt to improve accuracy of primary tumor delineation, ^{18}F-fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) has been incorporated in radiation treatment planning process. ^{18}FDG-PET-defined pTVs were consistently found to be significantly smaller compared with those based on pretreatment CT or MRI scans, but may offer the best approximation of the pTV as defined in the surgical specimen.[20,21] Although the PET-defined volume is highly dependent on the method of the PET signal segmentation tool,[22] fusion of PET and CT information can improve intraobserver and interobserver variability.[23,24] A drawback of PET is that it is not anatomically as accurate as CT or MRI to precisely define pTV.

Impact of primary tumor volume on local control

A number of authors have reported on the impact of tumor volume on outcome after definitive RT alone or combined with adjuvant chemotherapy with variable results.[10,12,13,19,25–39] In general, most authors have found that, depending on primary site, prognosis is inversely related to tumor volume.[25,26,30,31,34] Knegjens et al[28] reported on 360 patients treated with definitive CRT for locoregionally advanced SCCs of the oral cavity (22.4%), oropharynx (62.3%), and hypopharynx (15.2%) and followed for a median of 19.8 months. PTV was calculated on pretreatment CT or MRI; the median pTV was 28.7 cc (range, 2.1–187.7 cc). Multivariate analysis revealed a significant impact of pTV on local control. The authors observed that the hazard ratio for a local recurrence increased 14% for every 10 cc increase in pTV.

Mendenhall et al[6] reported on 404 patients treated with definitive RT alone (358 patients) or combined with adjuvant chemotherapy (46 patients) at the University of Florida and followed for a median of 3.5 years (range, 0.25–20.25 years). All living patients had a minimum 2-year follow-up. Pretreatment pTV was calculated on diagnostic CT. The number of patients with tumors in the various primary sites and the T classification distribution is depicted in Table 1. Forty-two of 45 patients with hypopharyngeal SCCs had primary lesions arising in the pyriform sinus. SCCs arising in the anterior tonsillar pillar were observed in 37 patients and in the soft palate in 12 patients. The 5-year local control rates were: tonsillar fossa/posterior tonsillar pillar, 86%; base of tongue, 84%; anterior tonsillar pillar/soft palate, 74%; supraglottis, 76%; glottis, 68%; and hypopharynx, 85%. Multivariate analysis of local control for the overall population revealed that the only parameter significantly related to this endpoint was T classification. Multivariate analysis stratified by primary site revealed that pTV significantly influenced local control for patients with SCCs of the supraglottis ($p = .0220$) and glottis ($p = .0042$) but not for those with SCCs of the tonsillar fossa/posterior tonsillar pillar ($p = .0892$), base of tongue ($p = .9493$), anterior tonsillar pillar/soft palate ($p = .5909$), and hypopharynx ($p = .2282$). A caveat is that the HR-HPV status of the tumors was not determined in this study. Because HR-HPV–related tumors are often smaller and more radiosensitive and chemosensitive compared with HR-HPV–negative tumors, it is possible that HR-HPV positivity masked the prognostic strength of pTV in oropharyngeal SCCs.[40]

Impact of primary site and primary tumor volume on local control

Nasopharynx. Sze et al[32] reported on 308 patients treated with definitive RT at the Pamela Youde Nethersole

TABLE 1. Primary site, primary tumor volume, and T classification distribution for 404 patients treated at the University of Florida.

	TF/PTP	BOT	ATP/SP	SGL	Glottis	HPX
No. of patients	69	72	49	114	55	45
T classification						
T1	3	3	1	4	0	6
T2	27	28	25	47	4	33
T3	25	23	16	51	47	4
T4	14	17	7	12	4	2
Median pTV, cc	9.2	14.8	5.2	5.4	2.9	3.9
pTV range, cc	0–187.5	1.5–235	0–99.9	0–65.8	0.8–8.2	0–.35.4

Abbreviations: TF-PTP, tonsillar fossa-posterior tonsillar pillar; BOT, base of tongue; ATP/SP, anterior tonsillar pillar/soft palate; SGL, supraglottis; HPX, hypopharynx; pTV, planning tumor volume.
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Eastern Hospital (Hong Kong) between 1998 and 2001. Pretreatment MRIs were used to calculate the pTV, including retropharyngeal node metastases. Patients received 70 Gy at 2 Gy per fraction; 128 patients (42%) received adjuvant chemotherapy. Median pTV was 22 cc (range, 1.4–218 cc). Median pTVs stratified by T classification were: T1, 2.7 cc; T2, 13.2 cc; T3, 28.1 cc; and T4, 65.5 cc. Median follow-up was 1.9 years (range, 0.1–3.9 years). The 3-year local control rates were 97% for patients with pTVs <15 cc and 87% for those with pTVs ≥15 cc ($p < .01$). Multivariate analysis revealed that pTV significantly impacted local control ($p < .01$). The authors estimated that the risk of a local recurrence increased approximately 1% for every 1 cc increase in pTV.

Chua et al[33] reported on 116 patients treated at the Queen Mary Hospital (University of Hong Kong) with definitive RT alone for T1 (67 patients) and T2 (49 patients) nasopharyngeal carcinomas between 1989 and 1991. Sixty-eight patients had a clinically negative neck (cN0); the remainder had N1 neck disease. Pretreatment CTs were used to calculate the pTVs. The median pTVs were: T1, 7.6 cc (range, 1.3–29.1 cc); and T2, 22.7 cc (range, 5.7–75.5 cc). The 5-year local control rates were: pTV ≤15 cc, 93%; and pTV >15 cc, 82% ($p = .033$).

Oropharynx

Chao et al[41] reported on 79 patients with SCC of the oropharynx, treated with definitive or postoperative intensity-modulated radiation therapy (IMRT; 17 of them also received platinum-based chemotherapy), between 1997 and 2001 at the MD Anderson Cancer Center. Thirty-one definitive IMRT patients were included in the volumetric study. On multivariate analysis, pTV and nodal volume were recognized as independent factors determining locoregional control and disease-free survival.

Been et al[19] reported on 79 patients with oropharyngeal SCC treated with definitive RT at the University of Wisconsin between 1991 and 2005. PTVs were calculated on pretreatment CTs by 2 observers. The mean pTV was 13.13 cc (range, 0.27–77.76 cc). Follow-up ranged from 4.9 to 165.8 months (median, 30.1 months). PTV did not correlate significantly with locoregional control. Locoregional control was significantly lower for patients with T4 cancers compared with those with T1 to T3 SCCs.

Hermans et al[36] reported on 112 patients with tonsillar SCCs treated with definitive RT and followed for 33 months. PTVs were calculated on pretreatment CTs. PTV was found to significantly predict local control when stratified by quartiles ($p < .05$) but not within T2 to T4 cancers. Multivariate analysis revealed that T classification significantly impacted local control ($p = .02$), whereas pTV did not significantly impact this endpoint.

Nathu et al[39] reported on 114 patients with T2 to T4 oropharyngeal SCCs treated at the University of Florida between 1983 and 1995 with definitive RT alone (102 patients) or preceded by 2 to 3 cycles of induction chemotherapy (12 patients). PTVs were calculated on pretreatment diagnostic CT scans. All survivors had a minimum 2-year follow-up. Multivariate analysis revealed that T classification significantly impacted local control ($p = .02$), whereas pTV did not significantly influence this endpoint ($p = .10$).

Lok et al[42] reported on 340 patients with oropharyngeal SCC, treated with IMRT in combination with platinum-based chemotherapy in the majority of them, between 1998 and 2009 at the Memorial Sloan–Kettering Center. The pTV was calculated using original RT plans in which the gross tumor volumes were contoured based on all available imaging and clinical examination. Large-size pTV (>32.79 cm^3) and advanced T classification tumors were found significantly associated with local failure when using univariate competing risks regression models; multivariate analysis was not performed because of the low number of local failure events. Furthermore, pTV was identified as an independent risk factor (together with N classification) for distant control and overall survival.

Supraglottis

Kraas et al[35] reported on 28 patients treated with definitive RT for supraglottic SCC at Wake Forest University between 1991 and 1997. PTVs were calculated on pretreatment CTs. Follow-up ranged from 20 to 58 months. pTVs ranged from 0 to 68.6 cc with a median of 3.1 cc. The 2-year local control rates were: pTV <8 cc, 70%; pTV >8 cc, 20%; and overall, 61% ($p = .0077$).

Hermans et al[37] reported on 103 patients treated with definitive RT for supraglottic SCC and followed for an average of 3.4 years. PTVs were determined based on pretreatment CTs. Multivariate analysis revealed that preepiglottic space invasion ($p < .01$) and subglottic extension ($p < .01$) significantly influenced local control. Although pTVs significantly impacted local control in the

univariate analysis ($p = .0023$), it was not found to be significant in the multivariate analysis ($p = .3288$).

Mancuso et al[13] reported on 63 patients treated with definitive RT for supraglottic SCC at the University of Florida between 1982 and 1991. The T classification distribution was as follows: T1, 1 patient; T2, 23 patients; T3, 37 patients; and T4, 2 patients. PTVs were calculated on pretreatment diagnostic CTs. Patients were followed for a minimum of 2 years or until local recurrence. Local control versus pTV revealed: $<$ 6 cc, 34 of 38 patients (89%); and $\geq$6 cc, 13 of 25 patients (52%; $p = .0012$). The overall local control rate was 47 of 63 patients (75%). Local control with preservation of laryngeal function was obtained in 44 of 63 patients (70%). Local control with preservation of a functional larynx versus pTV was obtained in 34 of 38 patients (89%) with pTVs $<$6 cc compared with 10 of 25 patients (40%) with pTVs $\geq$6 cc ($p = .00004$). Multivariate analysis of local control ($p = .0005$) and local control with a functional larynx ($p = .0001$) revealed that both of these endpoints were independently impacted by pTV, whereas neither were significantly influenced by T classification, N classification, preepiglottic space invasion, sex, or cord mobility.

Glottis

Pameijer et al[43] reported on 42 patients with T3 fixed cord glottic SCCs who were treated with definitive RT at the University of Florida between 1980 and 1993. PTV was calculated on pretreatment diagnostic CTs. Patients were followed for a minimum of 2 years or until local recurrence. Median follow up was 51 months (range, 4 months to 14 years). Local control after RT was observed in 30 of 42 patients (71%). Four patients underwent a total laryngectomy for a suspected local recurrence versus necrosis and had no pathologic evidence of persistent SCC so that 26 of 46 patients (62%) had local control with laryngeal preservation. Local control with laryngeal preservation was observed in 22 of 26 patients (85%) with pTVs $\leq$3.5 cc compared with 4 of 16 patients (25%) with pTVs $>$3.5 cc ($p = .0002$).

Pyriform sinus

Pameijer et al[38] reported on 23 patients with T1 (5 patients) or T2 (18 patients) SCCs of the pyriform sinus treated with definitive RT at the University of Florida between 1984 and 1993. PTVs were calculated on pretreatment diagnostic CTs. Patients were followed for a minimum of 2 years or until local recurrence. Local control was observed in 18 of 23 patients (78%): 17 of 19 patients (89%) with pTVs $\leq$6.5 cc compared with 1 of 4 patients with pTVs $>$6.5 cc ($p = .021$). Bulk disease at the apex ($\geq$10 mm) was also associated with a decreased probability of local control ($p = .027$). However, an update of the University of Florida data with 45 patients (42 of 45 patients had pyriform sinus primary sites) revealed no significant impact of pTV on local control ($p = .2282$) after definitive RT for hypopharyngeal SCCs.[6]

Further developments

In recent years, some refinements have been proposed in order to more accurately predict the outcome of patients after definitive RT based on pTV. In general, they are preliminary studies that need further validation.

Metabolically active tumor volume has been measured on pretreatment PET scans in patients treated by CRT. Seol et al[44] reported a relationship between ^{18}FDG-PET maximum standardized uptake value and the metabolic tumor volume with the progression-free survival and overall survival. A higher metabolic tumor volume of 9.3 cm was significantly associated with an increased risk of recurrence (2.19-fold; $p = .006$) and death (1.62-fold; $p = .051$).

Based on the relative radioresistance of hypoxic tumor cells to RT, the prognostic impact of the hypoxic tumor volume has been studied by Dunst et al.[45] The total tumor volume was calculated on pretreatment CT scans, and, in addition, all patients underwent measurement of tumor oxygenation by pO2 histography. The hypoxic tumor volume was defined as the product of the total tumor volume and the relative frequency of pO2 readings $<$5 mm Hg. Total tumor volume had a significant impact on survival, and the hypoxic tumor volume was also significantly different in patients who had died compared to surviving patients (11 vs 22 cm^3; $p = .009$), whereas the nonhypoxic tumor volume was not prognostically significant. Although the total tumor volume is a major prognostic factor, its impact may be dependent on hypoxic tumor volume.

CONCLUSIONS

The reproducibility of pTV calculations likely is influenced by the imaging modality and the experience and number of observers. The preferred imaging modality is probably contrast-enhanced diagnostic pretreatment CT using a minimum number of experienced observers.

The impact of pTV on local control varies with the primary site and is likely related to the radioresistance of the SCCs. Size for size, glottic and, to a lesser extent, supraglottic SCCs are probably more radioresistant than oropharyngeal SCCs and, thus, local control after RT is influenced to a greater degree by pTV for the former compared with the latter. Other parameters, such as HR-HPV and smoking status, also impact the likelihood of local control after RT for patients with oropharyngeal SCCs, which may mitigate the impact of pTV for at least those who are HR-HPV positive. The N classification likely impacts the probability of regional control, and, thus, locoregional control, but probably has little impact on local control.

Finally, the threshold at which local control decreases with increasing pTV probably varies from one institution to the next depending on how pTVs are calculated and would best be determined based on pTV outcome data from the institution in question. This would be most useful for patients with glottic and supraglottic SCCs and possibly, to a lesser extent, pyriform sinus cancers.

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