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Current Perspective

Elective unilateral nodal irradiation in head and neck squamous cell carcinoma: A paradigm shift

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Abstract There is a long-standing convention to irradiate the great majority of head and neck squamous cell carcinoma (HNSCC) electively to both sides of the neck, to reduce the theoretically increased risk of contralateral regional failure (cRF). With the currently available diagnostic imaging techniques this treatment paradigm means, in our opinion, an overtreatment in considerable proportion of these patients. From all the published studies (n = 11, with 1116 patients treated in total), the incidence of cRF in patients with oropharyngeal cancer treated to one side of the neck is 2.4%. The incidence was higher in patients with tumours involving the midline (12.1%). The low incidence of cRF was also seen in patients with HNSCC treated by local excision combined with unilateral neck dissection or sentinel node procedure. It seems clear from the aggregated data of these studies that a less conservative approach with regard to the selection of patients for unilateral elective nodal irradiation is justified. The fear of leaving the contralateral neck untreated in well-selected groups of patients with HNSCC needs nowadays to be mitigated since the incidence of cRF in lateralised tumours extending to but not crossing the midline is low. Furthermore, the obviously improved diagnostic imaging nowadays could help us to guide the selection of considerable proportion of patients with lateralised HNSCC for unilateral elective nodal irradiation with significant reduction of radiation-related toxicity and improved quality of life.

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Head and neck squamous cell carcinoma (HNSCC) has a strong tendency to metastasize to the regional lymph nodes (LNs) because of the rich regional lymphatic network. Regional metastasis is an important prognostic factor for outcome in HNSCC [1]. Although lateralised HNSCCs have a relatively orderly spread to cervical LN's [2], data about the pattern of cervical LN metastases to the contralateral neck is scarce. Because of these facts, there is a long-standing empirical convention within the head and neck radiation oncology community to irradiate both sides of the neck electively in almost all HNSCCs, with the exception of T1 laryngeal and very lateralised tonsillar fossa cancer (TFC). This treatment paradigm was based on the work of Lindberg *et al.* [3] in the sixties and seventies and stems from the era where nodal staging was exclusively based on clinical examination. The currently used diagnostic imaging techniques such as ultrasound, CT scan, (diffusion-weighted)-MRI, FDG-PET, and sentinel node biopsy have significantly improved the accuracy and reliability of nodal staging. Patients with N0, N1 or N2a disease from that time period will nowadays frequently be diagnosed as having N2b or N2c disease. Despite the fact that Perez *et al.* [4] showed in the late nineties a low incidence of contralateral regional failures (cRFs; around 8%) in T1–2 TFC, the empirically adopted treatment paradigm of bilateral elective nodal irradiation (ENI) has hardly changed. To date, patients with hypopharyngeal (HPC), laryngeal (LC; except T1) and the great majority of oropharyngeal cancer (OPC) are treated bilaterally. This is, in our opinion, an over-treatment in a considerable proportion of these patients. Therefore, we reviewed the published literature where the incidence of cRF in unilaterally treated OPC is reported and try to generate conclusions with regard to the possible risk factors for cRF.

The main concern when excluding the contralateral N0 neck from the ENI in HNSCC primarily treated with radiotherapy is the potential increased risk of cRF. Although no randomised controlled trials are conducted to compare the outcome of unilateral versus bilateral ENI, there is, however, slowly growing evidence in the literature [5–15] supporting the concept of unilateral nodal irradiation (UNI) in well-lateralized OPC with very limited risk of cRF.

Table 1 shows an overview of all published studies where unilateral ENI was applied in OPC. In these studies [5–15], 1116 patients were treated to the ipsilateral neck only between 1970 and 2014. The incidence of cRF was on average 2.4% (range 0–5.9%). Although in these studies patients with all T- and N-stages were treated, none of these studies showed a significant correlation between cRF and T-stage or N-stage of the ipsilateral neck. Even in studies where patients with involvement of midline structures were treated unilaterally [5,12,13], the incidence of cRF was only 12.1%. The drawbacks of this review are well-recognised by the authors. Most of these studies are retrospective and patients are treated within four decades in which radiation technology has evolved from 2D to 3D to intensity-modulated radiotherapy. Around 50% of these patients were treated with 2D techniques, where the contralateral neck can be treated, not-intentionally, to dose levels which might be enough to sterilise the microscopic disease. However, the incidence of cRF was not significantly increased by the use of conformal techniques in recently treated patients. Furthermore, no correlation between cRF and chemotherapy use was reported in the reviewed literature. Most of these patients have low-stage disease without indications for chemoradiation.

The incidence of contralateral metastasis is reported to be higher in OPC treated by resection of the primary tumour and bilateral neck dissection (ND). In the study of Olzowy *et al.* [16], bilateral metastasis was found in 20% of OPC patients from all subsites and T-stages. Interestingly, the incidence was higher in T2 and T3, compared with T4. This might mean that T2–T3 is approaching but not crossing the midline might have a higher chance of contralateral metastasis, compared with lateralised T4 not crossing the midline. Lim *et al.*

Table 1
The incidence of contralateral regional failure in patients with oropharyngeal cancer in the published literature (n = 1116 in aggregate).

Author (years of treatment)	Sample size	T & N stage	FU time	nMID (n=)	cRF nMID n (%)	MID involved (n)	cRF wMID n (%)	cRF total n (%)
O'Sullivan [5] 1970–1991	228	T1–4 N0-2b, N3	68 months	209	5 (2.4%)	19	3 (15.7%)	8 (3.5%)
Al-Mamgani [6] 2000–2011	185	T1–3 N0-2b	49 months	185	2 (1.1%)	No		2 (1.1%)
Jackson [7] 1975–1993	178	T1–4 N0-2b, N3	60 months	178	4 (2.2%)	No		4 (2.2%)
Lynch [8] 1995–2011	136	T1–3 N0-2b, N3	50 months	136	8 (5.9%)	No		8 (5.9%)
Chronowski [9] 1970–2007	102	T1–2 N0-2b	39 months	102	2 (2%)	No		2 (2%)
Kennedy [10] 1984–2012	76	T1–2 N0-2b	85 months	76	1 (1.3%)	No		1 (1.3%)
Dan [11] 2003–2014	61	T1–3 N1-2b	37 months	61	1 (1.6%)	No		1 (1.6%)
Liu [12] 1990–2002	58	T1–4 N0-2b, N3	102 months	51	0 (0%)	7	0 (0%)	0 (0%)
Jensen [13] 1998–2002	40	T1–3 N0-2b, N3	74 months	33	0 (0%)	7	1 (14.2%)	1 (2.5%)
Kagei [14] 1989–1996	32	T1–4 N0-2b, N3	44 months	32	0 (0%)	No		0 (0%)
Koo [15] 2003–2011	20	T1–3 N0-2b	64 months	20	0 (0%)	No		0 (0%)
Total	1116			1083	23 (2.2%)	33	4 (12.1%)	27 (2.4%)

Abbreviations: T & N stage: tumour and nodal stage; FU: follow-up; MID: midline involved; n: number of patients; cRF: contralateral regional failure; cRF nMI: contralateral regional failure in patients with no midline involvement; cRF wMI: contralateral regional failure in patients with midline involvement.