The role of radiotherapy +/- chemotherapy in oral cavity cancer

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Background

- head and neck cancer is the 5th most common cancer worldwide
- worldwide oral cancer accounts for ~40% of all head and neck cancer
- 5% of adult cancers in western world are mucosal head and neck (HN) cancers
- larynx, oropharynx and oral cavity are all common sites for a HN cancer
- 90-95% of oral cavity cancers are squamous cell carcinomas (SCC)
- most (but not all) patients are smokers (or ex) and drinkers, aged >60 years
- small subset (5-10%) that are younger (<40-50 yrs) many without significant exposure to cigarettes/alcohol
- the two most common subsites for an oral cavity SCC are the anterior tongue and the floor of mouth in western world
- India and SE Asia buccal SCC is a more common subsite secondary to betel nut chewing
- lip SCC is related to sun exposure (at least in Australia) and although often considered an oral cavity cancer is essentially a subsite of non melanoma skin cancer
- Human Papilloma Virus (HPV) oncogenic subtypes 16 and 18 associated with oropharyngeal carcinomas in a subset of patients, often younger (eg 55 yrs old) and without significant smoking/alcohol intake. Prognosis is often better compared with similar stage smoker/drinkers.
- symptoms have often been present for many months and the location in the oral cavity may provide the opportunity for an early visual diagnosis
- neck lump is a common reason for presentation, often initially misdiagnosed as benign

- many patients will subsequently present with advanced stage disease (T3/4 and /or N1-3) despite the potential for early diagnosis

Diagnosis

- biopsy confirmation is mandatory DD = carcinoma, sarcoma, lymphoma, melanoma or benign
- thorough exam of upper aerodigestive tract to exclude another primary SCC, this may involve nasendoscopy in clinic and/or examination under anaesthesia (EUA)
- CT with contrast scan in selected cases (usually not that helpful in early stage disease)
- chest x-ray to exclude synchronous lung cancer (<5% of patients)
- OPG and dental assessment very important because of the high dose (>60Gy) of radiotherapy the mandible may receive and also long term xerostomia. Patients with infield mandibular molar teeth will usually have these extracted. There should be a ~2 week period from extraction to radiotherapy to allow for healing (ideally)
- baseline bloods if chemotherapy is considered, or otherwise indicated (eg liver function in alcoholics)
- metastatic spread beyond the HN region at diagnosis is uncommon and therefore CT scans of the chest or abdo/pelvis should not be routinely performed in all patients. Patients with advanced T4 primaries and/or N2-3 nodal disease are at higher risk of having subclinical distant disease, although chest/abdo CT scans still often NAD
- Positron Emission Tomography (PET) scans offer whole body cancer screening and are helpful in assessing response post treatment (performed at ~3 months). Useful in setting of unknown primary in conjunction with other investigations. But role as a routine pre-treatment investigation with a known primary is unclear (in addition to usual investigations). Useful in recurrent setting to determine if distant metastases are also present
- discussion of patient in multidisciplinary HN clinic prior to a management decision being made

Prognosis

- increasing TNM stage at presentation is associated with a worse outcome
- the presence of nodal metastases and extranodal extension are powerful prognosticators
- in early stage disease tumour thickness is an independent predictor of outcome
- anterior tongue/floor of mouth SCC >5mm thick have an incidence of >20-30% of occult spread to upper cervical lymph nodes

Treatment

- early stage (T1/T2 N0) oral cancer should be treated with single modality, usually surgery thus avoiding the late consequences of radiotherapy (especially xerostomia)
- clinically early stage oral SCC often require treatment to ipsilateral lymph nodes even when clinically node negative
- advanced stage (T3/4 N1-3) oral cancer is usually treated with a combination of initial surgery and adjuvant (post operative) radiotherapy
- surgery alone in advanced disease is associated with a high rate of recurrence as a result of residual microscopic cancer
- very advanced and inoperable oral cancers may be treated with a combination of cisplatinum based chemotherapy and radiotherapy (surgery may rarely follow)
- cisplatinum and 5FU are the most commonly used agents, usually only cisplatinum is given in conjunction with radiotherapy because of added mucosal toxicity of 5FU

Surgery

- aim is to excise primary cancer and (if relevant) any sites of potential lymph node spread (usually first echelon nodes) (eg partial glossectomy and upper neck dissection)
- functional outcome (eg swallowing) post surgery is always an important consideration

- if adequate oncological excision margins are achieved and lymph nodes are not involved the risk of recurrence is low (<10-15%) and further treatment is usually not indicated

Radiotherapy

- radiotherapy is given by a linear accelerator (LA) and is often referred to as external beam radiotherapy (EBRT)
- linear accelerator generate photons (very high energy and penetrating x-rays)
- a single daily dose of radiotherapy is referred to as a fraction
- radiotherapy is measured in Gray (Gy), a typical daily fraction is 2Gy
- a total dose of 60-70Gy (radical treatment) is delivered in small divided fractions
- brachytherapy is another type of radiotherapy delivered by implanting a radioactive source in the cancer (limited role, rarely utilised in Australia/USA, more common in Europe/UK)
- radiotherapy alone is rarely used either in early resectable cancer (best treated by surgery) or more advanced but still operable cancer (best treated by radiotherapy + chemotherapy)
- main role is therefore that of reducing risk of recurrence after surgery in patients with unfavourable pathology (implies that residual microscopic cancer remains)
- radiotherapy and chemotherapy may be given together (without surgery) in advanced and inoperable patients (if suitable)
- a typical course of external beam radiotherapy will take 6-7 weeks of outpatient daily week day treatment, taking only a few minutes to deliver each day
- altered fractionation radiotherapy usually refers to radiotherapy given more than once daily and is a way to improve outcome (and also toxicity)
- a definitive course of radiotherapy can only be delivered once, this is an important consideration in a younger patient who may develop another head and neck cancer in years

to come

- Intensity-modulated radiotherapy (IMRT) aims to deliver 3D very accurate conformal treatment with techniques that can markedly reduce the dose to normal structures (eg parotid gland) and increase the tumour dose. The aim is to improve outcome (i.e. survival) and decrease late toxicity (eg xerostomia). However this technology is resource intensive and is not currently widely available to all HN patients.

Adjuvant radiotherapy (post operative)

Primary site indications (usually a combination of unfavourable variables)

- close or positive margins (if re-excision is not considered)
- deeply invasive, high grade cancer, perineural or lymph vascular invasion

Lymph node (neck) indications

- multiple LNs involved, only one LN but >3cm in max dimension
- only one LN <3cm but with extranodal spread
- indications for recommending adjuvant radiotherapy are usually multiple i.e. primary site and the neck (eg close margin and multiple LNs involved)
- radiotherapy is recommended if unfavourable pathological features are present because these will put the patient at risk of recurrence (>20%)
- recurrent oral cancer carries a very poor prognosis and is more often than not inoperable and incurable, all efforts are directed at preventing recurrence
- radiotherapy will reduce the rate of recurrence by ~50% ie if the absolute risk is 30% radiotherapy will reduce this to around 15%

Adjuvant chemo/radiotherapy (post operative)

- two published randomised trials suggest a better outcome in patients with

unfavourable features (multiple nodes, extranodal spread) with the addition of cisplatinum chemotherapy and adjuvant radiotherapy. Toxicity is an issue. Recent update suggests only selected patients with positive margins and/or extranodal spread should be offered this.

Definitive radiotherapy and chemotherapy

- concept of organ preservation using radiotherapy and concomitant chemotherapy is more relevant to advanced larynx and hypopharynx SCC
- however, very advanced lesions eg T4 larynx SCC are often better approached with laryngectomy + RTx since function after RTx/CTx is often very poor
- non-surgical approach in patients with oropharyngeal SCC (tonsil, tongue base, soft palate)
- if inoperable, a patient may still be potentially curable with a combination of radiotherapy and chemotherapy (5 year survival 10-30%)
- radiotherapy alone may be indicated if chemotherapy is contraindicated
- chemotherapy alone may be given to palliate in the setting of recurrent cancer after previous high dose radiotherapy

Cetuximab (Erbitux)

- Monoclonal antibody against EGFR receptor
- enhances radiotherapy cytotoxicity
- better toxicity profile compared with radiotherapy and chemotherapy
- reports of severe cutaneous reactions
- current role unclear

Radiotherapy side effects

Acute side effects (during radiotherapy)

- xerostomia (dry mouth/throat) and loss of taste secondary to decreased saliva
- mucostis (painful ulceration of mucous membranes starting at week 2-3 of radiotherapy)
- skin reactions (moist desquamation similar to moderate sunburn type reaction)
- loss of taste (usually returns after 2-3 months)
- fatigue and tiredness
- weight loss of 5-10% of body weight by end of treatment, some units will preemptively insert PEG feeding tubes but are associated with side effects and expense

-occasional patient requires hospital admission for rehydration, tube feeding and pain management

Majority of acute reactions will resolve in 4-6 weeks (occasionally longer)

Late side effects (months to years after radiotherapy)

- some degree of xerostomia is permanent (implications for long term dental consequences)
- taste may never return completely to pretreatment state
- impaired swallowing (pharyngeal fibrosis) in combination with effects of any surgery
- small risk of osteoradionecrosis (ORN) of the mandible (<5%) and bone exposure more so in patients that continue to drink and smoke

Follow up

- every 3-4 months for first 2 years and every 6 months for another 2-3 years
- 20% will continue to smoke and be at high risk for a recurrence or second primary
- by 5 years 20-25% of patients will have developed a second malignancy, most will be smoking related i.e. another head and neck cancer, lung cancer, esophageal, bladder…

- despite combined radical treatment many patients with advanced oral cancer will still recur, most often in the head and neck region
- most, but not all, recurrences (90%) will have occurred by 2 years, but follow up usually continues to 4-5 years
- close follow up has the potential to detect an early recurrence or second primary, although patient will usually self detect relapse rather than clinicians at follow up
- in practice many patients present with incurable relapse or advanced second cancers
- many succumb to lung (CAL), heart (AMI), neurovascular (CVA) or liver disease secondary to ongoing and/or previous smoking and drinking