原文題目(出處)：	HPV & head and neck cancer: a descriptive update. Head Neck Oncol 2009; 1:36.
原文作者姓名：	Goon PKC, Stanley MA, Ebmeyer J, Steinsträsser L, Upile T, Jerjes W, Bernal-Sprekelsen M, Martin G, Sudhoff HH
通訊作者學校：	University of Cambridge, Cambridge, UK
報告者姓名(組別)：	吳筱婷 (Intern F組)
報告日期：	2010.03. 08

內文：

Introduction and epidemiology

- The incidence of head and neck squamous cell carcinoma (HNSCC) has been gradually increasing over the last 3 decades.
  - 5th leading cause of cancer by incidence
  - 6th leading cause of mortality in the world
  - In 2002, 405,000 were reported ; 211,000 deaths occurred worldwide
  - In 2009, 5000,000 cases, only 20-50% will survive for 5 years
  - Risk factor so far identified are tobacco and alcohol
- Cannabis has been postulated to have a role in the pathogenesis of HNSCC.
  - Cannabis smoke is fairly similar to tobacco smoke but actually has a greater concentration of the aromatic poly-carbon carcinogens found in cigarette smoke.
  - Cannabis usually smoked unfiltered, allowing a greater concentration of toxin unfettered access to the mucosal surface.
  - Only one study of note has shown a statistically significant increased risk of head and neck cancer.
  - Nearly all the studies have limitations of small sample size and insufficient statistical power.
- Diet is another factor implicated in the aetiology of HNSCC, especially a low consumption of fibre and vitamins.
- Poor oral hygiene and poor dentition have also been like to an increased risk of developing oro-pharyngeal cancer.

Human papillomavirus (HPV) as a risk factor

- Recent data have now attribute a viral aetiology to a subset of head and neck cancers; the human papillomavirus(HPV).
- 1983 by Finnish team noted that 40% of the cancers in their study contained histological and morphological similarities with HPV-associated lesions.
- Several studies indicate that oral HPV infections is likely to be sexually acquired.
- Syrjanen's observations in 1985, there have been numerous publications studying HPV DNA detection in HNSCC with rates varying from 0% ~100% of tumour studied
- In 2005 conducted a systematic meta-analysis to reviews the available literature in the field and ascertain the world wide prevalence of HPV in HNSCC.
  - Using PCR detection from 26 countries
  - 5046 cases of SCC; 2642 oral cancers; 969 oropharyngeal cancers and 1435 laryngeal cancers
  - Overall prevalence pf HPV in HNSCC was estimated at 26%.
  - HPV 16 was by far the commonest subtype in all types of HPV+ cancers. HPV 18 was the next.

Insights into the molecular mechanisms of HPV carcinogenesis

- The dominance of HPV 16 in HPV+ HNSCC is even greater than that seen in

cervical carcinoma of total worldwide cases.

- It has been shown that these subtypes (particularly 16) are able to transform and immortalize cell in vitro.
- These effects are predominantly due to the E6 and E7 oncogenes, which bind and enhance degradation of P53 and RB tumour suppressor genes respectively. There is evidence that immortalization of oral kerationocytes and epithelial cells occur quite readily.
- Integration usually lead to disruption and/or deletion of HPV E1 or E2 open reading frame (ORF), which are important for viral replication and transcription.
  - E2 functions also as repressor of E6 and E7 and disruption of E2 activity allows increased E6 and E7 expression, thus maintaining the immortalized pheno type.
- Mellin et al concluded that the data suggested that a higher viral load could be a favourable prognostic indicator.
- Koskinen et al reported that the median copy number of E6 DNA was about 80,000 fold higher in tonsillar cancers as compared to non-tonsillar head and neck cancers. Episomal DNA had larger tumours than patients with mixed or integrated forms of viral DNA.
  - Higher copy number of episomal viral DNA was able to induce more rapid growth, perhaps by higher expression of the viral oncogenes.
- Weinberger et al demonstrated that HPV 16 viral load and p16 expression could be used to classify head and neck cancers into 3 distinct profiles :
  - Class I : HPV- , p16 low
  - Class II : HPV+ , p16 low
  - Class II : HPV+ , p16 high

  → Class III tumours had a significantly increased 5 year survival , increased disease free survival rate and decreased local recurrence rate, compared to tuours in the other 2 classes.

Clinical implications of HPV+ head and neck cancers

- Strong evidence suggests that HPV+ status is an important prognostic factor associated with a favourable outcome in head and neck cancers.
- Maura Gillison's lab demonstrated that patients with HPV+ tumours had better response rates after induction chemotherapy (85% vs 55%) and after chemoradiation treatment(84% vs 57%) compared to patients with HPV- tumours.

→ Associated with a better response to current treatment regimens

→ Associated with a much improved survival rate, and risk of progression compared to HPV- tumours status.

Current treatment options available for head and neck cancer

Treatment options for early stage disease

- Approcimately 30%~40% of patients present with early stage I/II disease.
- These patients in general are treated with curative intent using either single modality treatments or using radiation or surgery alone. Because both modalities result in similar rates of local control and survival, the choice of treatment is usually based upon an assessment of functional outcomes and competing morbidities.
- Early stage disease is associated with an excellent prognosis, these patients are still at high risk for recurrence and second primary tumours and need close monitoring.

Potentially respectable local advanced disease

- Treatment goals for patients with respectable locally advanced disease are to

maximize cure while maintaining functional status through organ preservation.

- Surgery combined with postoperative radiotherapy, especially when risk factors, such as positive surgical margins, perineural or lymphovascular involvement, bone or cartilage invasion, T3/4 or nodal disease (N2-3) or extracapsular lymph node extension were present.

Definitive Radiochemotherapy

- A nonoperative approach is favored for patients in which surgery followed by either radiation alone or radiochemotherapy may lead to severe functional impairment.
- The feasibility of non surgical approach in this situation was proven by the RTOG 9111 trial.
  - 547 patients with stage III and IV supraglottic or glottic cancer into 3 arms
  - Radiotherapy alone; concurrent radiochemotherapy with high dose cisplatin or induction chemotherapy with cisplatin and fluorouracil followed by radiation.
  - Preservation of the larynx and local control were best achieved with concurrent chemoradiotherapy, which led to an absolute reduction of 43% in the rate of laryngectomy.
  - Overall survival was not different in the three arms.
  - This study established concurrent chemoradiotherapy as accepted standard for patients with advanced laryngeal cancer who want to preserve their larynx.
  - However toxicity remains a significant problem with this approach.

Definitive Radiochemotherapy

- To improve the limited survival rates in patient with bone/cartilage invasion or gross organ destruction, 3 studies have been performed to determine whether the addition of cisplatin to radiotheraphy improves the outcome, as compared with radiotherapy alone.
- Concurrent chemoradiothraphy only reduced the risk of loco-regional recurrence without differences in survival.
- However both studies reported a significant increase in toxicities, such as mucositis, bone marrow suppression and fibrosis, so that this aggressive treatment should be reserved for patients with high-risk features.
- Patient with comorbity or low risk features should received postoperative radiation alone.

Induction chemotherapy

- With combined modality treatment local control rates have risen, but survival still remains poor, since distant metastasis have become a major site of fatal recurrence.
- Systemic chemotherapy has been shown to decrease the risk of distant metastasis, several study groups tested induction chemotherapy followed by radichemotherapy in patients with locally advanced HNSCC.
- A meta-analysis showed a 5% survival benefit for induction chemotherapy using cisplatin and fluorouracil.
- However the most important question whether induction chemotherapy followed by radiochemotherapy is better than radiochemotherapy alone remains open until results of ongoing trials addressing this problem available.

Recurrent and distant metastatic disease

- Up to 50% of patients who die from HNSCC have locoregionally recurrent disease as the sole site of failure.

- If surgical salvage is not feasible alternatives include additional irradiation or palliative chemotherapy.
- Palliative treatment strategies should focus not only response rates but also on toxicities and life quality aspects.

Therapies targeting Epidermal Growth Factor Receptor

- The epidermal growth factor receptor (EGFR), has been identified as therapeutic target for HNSCC and several other malignomas.
- Evaluation of EGFR-targeted therapies in HNSCC-patient was based on the observation that EGFR is highly expressed in many tumours and that EGFR overexpression was associated with reduced survival in several studies.
- For clinical use EGFR can be targeted either by antibodies recognizing or by EGFR tyrosine kinase inhibitors.

Anti-EGFR antibody theraphy

- Centuximab, a humanized mouse anti-EGFR IgGI monoclonal antibody, improved locoregional control and overall survival in combination with radiotherapy in locally advanced tumours.
- But the cost of some increased cardiac morbidity and mortality.

Summary

- The incidence of head and neck squamous cell carcinoma (HNSCC) has been gradually increasing over the last 3 decades.
- Human papillomavirus induces a subset of head and neck carcinomas
- Oral HPV infection is likely to be secuallly aequired
- HPV+ status is an important prognostic factor associated with a favourabe outcome.
- Anti-EGFR targeted therapy improves locoregional control and overall survival in combination with radiotherapy in locally advanced tumours.
- Detailed molecular characterization of signaling pathways in HNSCC tumours prior to therapy might help to define subpopulations of responsive patients

題號	題目
1	下列何者並非頭頸部放射線治療造成之副作用? (A) 黏膜炎 (B) 牙關緊閉(trismus) (C) 放射線骨壞死 (D) 過度流涎(excessive salivation)
答案(D)	出處：oral and maxillofacial pathology 2nd p261~264
題號	題目
2	下列何者最可能發生惡行變化? (A) 輕度上皮變異(mild epithelial dysplasia) (B) 中度上皮變異(moderate epithelial dysplasia) (C) 重度上皮變異(severe epithelial hyperplasia) (D) 上皮增生(epithelial hyperplasia)
答案(C)	出處：oral and maxillofacial pathology p343~345