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The Royal College of Radiologists is appealing against the guidance on Cetuximab in locally advanced head and neck cancer recently published by the National Institute for Health and Clinical Excellence (May 14, 2007).

The aspects of the guidance being appealed against are:

a) lack of sufficient understanding by the Committee of the difference between patient performance status and patient comorbidity and how this distinction impacts on patient management (3.6, 4.8, 4.10);
b) lack of appreciation by the Committee of why there is variation in radiotherapy fractionation practice and how this influences choice of treatment (3.6);
c) the Committee have exceeded their powers in recommending Carboplatin rather that Cetuximab in patients unsuitable for Cisplatin chemoradiotherapy (4.10);
d) the Committee has not sufficiently addressed expert advice that appropriate randomised controlled trials comparing chemoradiotherapy with Cetuximab plus radiotherapy would not be successfully carried out from methodological, clinical, ethical or funding reasons (4.6).

The grounds of this appeal are: 1) The Institute has prepared a FAD that is perverse in the light of the evidence submitted (a and b above); 2) The Institute has exceeded its powers (c and d above).

Basis of the appeal

A) The guidance fails to distinguish adequately between patient performance status and patient comorbidity. Comorbidity and functional status are independent prognostic factors in cancer patients (Extermann M, et al. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol* 1998; **16:** 1582–87.). The appraisal committee make an assumption that patients of good performance status (KP 80–100; WHO 0/1) "would be expected to be suitable for chemoradiotherapy" (section 3.6 of FAD). The appellants consider that 60% of patients (page 18 STA Merck response) considered unsuitable for Cisplatin chemoradiotherapy and given radiotherapy alone would be of good performance status. Consequently we refute the Committee's view (4.8) "that patients with lower performance status would form most, if not all of the population for whom chemoradiotherapy would be considered inappropriate in clinical practice".

NHS professionals (mostly head and neck clinical oncology experts) have listed in the STA the complex reasons why good performance status patients are sometimes considered unsuitable for Cisplatin chemotherapy, namely:

1. Previous history of vasculopathy (if patient has active angina we would not give Cisplatin or Cetuximab).
2. Heavy alcohol intake (makes toxicity from chemoradiotherapy unpredictable).
3. Asymptomatic renal impairment (Committee suggest we use Carboplatin which has a less satisfactory evidence base than Cetuximab).
4. Existing immunodeficiency (makes toxicity from chemotherapy unpredictable).
5. Social deprivation (lack of support in coping with toxicities from chemoradiotherapy).
6. Mental comorbidity (compliance issues and inability to cope with enduring toxicities from chemoradiotherapy).
7. Hearing impairment or patients having significant radiotherapy dose to the inner ear with resultant risk of sensorineural deafness and tinnitus (would be exacerbated by Cisplatin.)

The key issue here is that the Committee are putting the onus on the applicant (Merck) to demonstrate that a significant proportion of good performance status patients in the Bonner study had contraindications to chemoradiotherapy rather than accepting from a whole body of clinical experts that there would always be a significant proportion of good performance status patients whom clinicians/MDT consider unsuitable for chemoradiotherapy.

B). There is considerable ignorance in the Committee around radiotherapy fractionation issues. The principal themes from the Committee seem to be (i) the accelerated regime predominantly used in the Bonner study is not used in the UK; (ii) Cetuximab showed a benefit with this accelerated regime but there was little data for conventional fractionation, which is the dominant fractionation in UK practice.

The reason why conventional fractionation is dominant in UK practice is because chemoradiotherapy is the prevailing approach used for intensification. If the patient is of good performance status but considered unsuitable for chemoradiotherapy then intensification can still be achieved using radiotherapy alone by acceleration (often used in the UK) or hyperfractionation (patient inconvenience/logistics make this unpopular in the UK). Fortunately, the Bonner study used intensified radiotherapy for most patients and the benefit of Cetuximab was “over and above” that achieved with intensified radiotherapy. It has previously been highlighted that the local control benefit of accelerated radiotherapy plus Cetuximab compared to conventional fractionation only is likely to be at least as great as with chemoradiotherapy (using conventional fractionation) but with less enduring toxicity than with chemoradiotherapy.

Thus, the guidance should stipulate that if patients are of good performance status but unsuitable for chemotherapy then Cetuximab plus radiotherapy should be given with an accelerated regimen of radiotherapy (RTOG concomitant boost or DAHANCA both give 8–10% local control benefit over conventional fractionation). Although this approach constitutes an intensive treatment, it is generally acknowledged that the toxicities are more predictable than those from chemoradiotherapy with treatment related death unlikely (versus 4% for chemoradiotherapy).

C) The guidance exceeds its powers in advocating single agent Carboplatin (unlicensed for this usage) as the treatment of choice for patients of good performance status considered unsuitable for Cisplatin chemoradiotherapy. Carboplatin is currently used by some practitioners for the lack of an alternative, otherwise radiotherapy alone would be given.

The evidence base for Carboplatin is poor with almost all the single agent platin data being for Cisplatin:

(i) Much of the trial data with Carboplatin is using combination therapy (5FU or Taxane), thus is not relevant to this discussion.

(ii) Limited Phase 3 data used low dose daily Carboplatin which has not be adopted elsewhere (Jeremic B, et al. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomised trial. *Radiother Oncol* 1997; **43:** 29–37.).

(iii) “Promising” data is based on small Phase I/II studies (Osoba D, et al. Phase I study of concurrent carboplatin and radiotherapy in previously untreated patients with stage III and IV head and neck cancer. *Head Neck* 1991; **13:** 217–22; Orecchia R, et al. Concomitant radiotherapy and daily low-dose carboplatin in locally advanced, unresectable head and neck cancer. Definitive results of a phase I-II study. *Acta Oncol* 1994; **33:** 541–45; de Serdio JL, et al. Chemotherapy as a part of each treatment fraction in a twice-a-day hyperfractionated schedule: a new chemoradiotherapy approach for advanced head and neck cancer.*Head Neck* 1998; **20:** 489–96).

The benefits in loco regional control with Cetuximab and accelerated radiotherapy from the Bonner trial appear to be at least equivalent to Cisplatin and conventional radiotherapy; there is no data to suggest Carboplatin is equivalent to these.

D) The guidance again exceeds its powers in advocating trials of radiotherapy plus Cetuximab versus chemotherapy as it would be impossible to get agreement on appropriate trial design and/or funding to do this trial.

Option A
Accelerated RT schedule + Cetuximab v accelerated schedule + synchronous Cisplatin – latter would be considered too toxic; difference in tumour control likely to be very small – numbers required too large.

Option B
Accelerated RT schedule + Cetuximab v conventional RT + Cisplatin – would not be considered scientific (2 variables) and likely differences would be in late toxicity (would not be funded).

Option C
Conventional RT + Cetuximab v conventional RT + chemo – former would be regarded as substandard as Cetuximab does not increase mucositis; conventional RT is not longer optimum fractionation and randomised trial evidence confirms that acceleration gives better outcomes for EGFR positive cancer than conventional fractionation.

Post script
From the evaluation report (pp 108–113) the estimated number of patients eligible for Cetuximab plus radiotherapy is incorrect. The figures should be: of 100 patients with head and neck squamous cancer 55 have locally advanced disease (stages 3 and 4), 35 have primary non-surgical management, 18 of these 35 have chemoradiotherapy (51% page 111), 5 have palliation/supportive care only, 5 have radical radiotherapy only (fair performance status), leaving 7 who have radical radiotherapy only (good performance status but considered unsuitable for chemoradiotherapy due to comorbidity—ie, 7% of head and neck patients are best treated by Cetuximab and radiotherapy (not 1015/6449 as on page 113).

Members and Fellows of The Royal College of Radiologists