its transcriptional activity. Furthermore, p63-induced growth inhibition is markedly counteracted by mutant p53. Thus, inactivation of p53 family members may contribute to the biological properties of p53 mutants in promoting tumorigenesis and in conferring selective survival advantage to cancer cells.

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p53 diagnosis in human cancer: what utility?

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The tumour suppressor p53 is a phosphoprotein barely detectable in the nucleus of normal cells. Upon cellular stress, particularly that induced by DNA damage, p53 can arrest cell cycle progression thus allowing the DNA to be repaired or it can lead to apoptosis. In cancer cells bearing a mutant p53, this protein is no longer able to control cell proliferation, resulting in inefficient DNA repair and the emergence of genetically unstable cells. Three approaches can be used to test p53 alteration in human tumour: molecular, immunocytochemical and serological diagnosis. i) Molecular analysis DNA sequencing led to the determination of the exact mutational event that modified the p53 gene. ii) Immunocytochemical analysis p53 mutations induce a change in the conformation of the p53 protein leading to the stabilisation and the accumulation of p53 in the nucleus of tumoural cell. This observation has encouraged an intensive study of the expression of p53 protein by immunohistochemistry in a large panel of tumours, since there seems to be a good correlation between p53 gene mutation and protein accumulation iii) Serological analysis We demonstrate that p53-Abs are found predominantly in human cancer patients with a specificity of 96%. Such antibodies are predominantly associated with p53 gene missense mutations and p53 accumulation in the tumour. It has been demonstrated that this immune response is due to a self-immunisation process linked to the strong immunogenicity of the p53 protein.

The detection of p53 mutation in human tumours have been extensively studied for molecular epidemiology or for clinical evaluation in order to link p53 deficiency to therapy failure or prognosis. Due to an important heterogeneity in the methods used for the detection of p53 alteration, there is a huge controversy concerning the clinical value of p53 alteration. These points will be discussed in the view of recent information concerning p53: i) the inadequate strategy used by the majority of laboratories to analyse p53 status; ii) strong evidence in favour of the heterogeneous behaviour of various mutant p53 proteins; iii) discovery of p53 family members, p63/p73 and iv) association of codon 72 polymorphism (Arg/Pro) and specific properties of the protein. We will conclude with some recommendations concerning the strategy to be used for an unbiased analysis of p53 alterations in human tumours and its potential benefit in clinical practice.

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Predictive value of p53 alterations to therapy in cancer; critical evaluation of clinical and laboratory methods

Abstract not received.

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p53-induced apoptosis and new cancer therapy

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The p53 tumor suppressor protein inhibits tumor growth largely through its ability to induce apoptosis. p53 induces apoptosis through transactivation and transrepression of specific target genes. Around 50% of all human tumors carry p53 point mutations that disrupt p53:s specific DNA binding and thus p53-mediated target gene regulation.

Since p53 mutation is frequent in human tumors of various types, new therapeutic strategies based on restoration of wild type p53 function should be applicable to a large number of tumors. One such approach is pharmacological reactivation of mutant p53 proteins. Mutant p53 is often expressed at high levels in tumor cells and so mutant p53 reactivation should trigger massive apoptosis and eliminate the tumor. In order to identify low molecular compounds that can restore wild type function to mutant p53, we screened a chemical library from the National Cancer Institute. We identified one compound that was capable of inducing apoptosis in human tumor cells in a manner dependent on mutant p53 expression. This compound could restore the specific DNA binding and preserve the active conformation of mutant p53 proteins in vitro. Moreover, it restored both wild type p53 conformation and the transactivation function of mutant p53 in living cells. The molecule was able to reactivate a wide variety of tumor-derived mutant p53 proteins. In vivo experiments demonstrated inhibition of xenograft tumor growth with no apparent toxicity. This compound represents a first step towards the development of anticancer drugs that specifically target mutant p53.

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Improvement in tumour staging

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Overall prognosis of patients with oesophageal carcinoma remains poor, mainly due to the late presentation and advanced stage of the disease at the time of presentation.

The therapeutic option in oesophageal cancer management depends on the clinical staging and includes radical surgery in early disease, multimodal treatment schemes combining neo-adjuvant chemoradiotherapy followed by surgery in locally advanced disease and palliative treatment in cases of distant metastatic disease.

Over the last decades, clinical staging has improved since the introduction of CT-scan and transoesophageal endoscopic ultrasound (EUS). However, performing threefield lymphadenectomy we found that 20% of the patients with T3N1 adenocarcinoma of the distal oesophagus had unexpectedly positive lymphnodes in the cervical region.

As for the T-factor, EUS is especially valuable in assessing transmural extent of the tumour provided the tumour can be passed. The T-factor is often overestimated on CT-scan.

As for the local nodes (N1), CT-scan and EUS have a high sensitivity but a low specificity. Newer techniques, such as EUS guided biopsy aim to overcome the difficulties in differentiation between benign and malignant nodes.

Some centers propagate the routine use of minimally invasive surgical staging procedures such as thoracoscopy and laparoscopy in the evaluation of nodal involvement and allowing the detection of unimaged pleural or peritoneal disease. These techniques however are time consuming and have their own morbidity.

We evaluated the use of PET-scan in preoperative staging of oesophageal carcinoma (n = 74). The sensitivity and specificity for detection of stage 4 disease was statistically significantly better than for CT + EUS. The additional value in detecting stage 4 disease with PET-scan was 16%.

PET scan showed to have a low sensitivity (22%) in detecting locregional lymphnodes. For detection of metastatic lymphnode involvement however, the sensitivity of PET scan was 77% which was higher than the sensitivity of CT + EUS (46%).

PET scan has a high specificity, both for local lymphnode as for metastatic lymphnode involvement (90%).

We conclude that clinical staging for oesophageal cancer remains poor, probably because of the extensive and unpredictable lymphatic spread. PET-scan however has an important role in this staging. PET scan also seems to have an important role in assessing tumour response in induction treatment schemes.

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Surgery: extent of resection

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Overall prognosis in patients with carcinoma of the esophagus and GEJ remains poor mainly due to the late presentation and advanced stage at the time of diagnosis. Over the last decades postoperative mortality has substantially decreased from approximately 15% before the eighties to approximately 5% in high volume centers.

A complete resection (R0) is the goal of any surgery for cure. Much debate however persists on extent of surgery.

The options are standard resection, usually transhiatal versus extended resection and lymphadenectomy, mostly performed transthoracically. More radical surgery definitely results in better staging and prolonged tumour free survival. Although proof is lacking data from literature suggests higher cure rates after more extensive surgery with five year survival rates of approximately 35% after R0 resection, whereas reported 5-year survival rates after standard resection mostly are below 25%.