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## Systemic treatment of metastatic malignant melanoma

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**Chemotherapy:** Systemic therapy for melanoma, both as adjuvant therapy and for treatment of disseminated (stage IV) disease, remains unsatisfactory. Patients with high-risk or metastatic disease should be considered for enrollment in investigational studies. Few chemotherapeutic agents have demonstrated antitumor activity against metastatic melanoma. In a review of phase II trials, only 4 of 30 drugs that were tested demonstrated a response rate greater than 18% in melanoma patients. The best-studied single agents for treatment of melanoma are Dacarbazine (D) (20% RR), Fotemustine (F) (24% RR), Vindesine (V) (14% RR) and Cisplatin (P) (23% RR).

**Combination:** The role of combination chemotherapy in treatment of advanced melanoma is not entirely clear. The most active combination regimens (FDV) (32% RR) and (PDV) (32% RR).

**Biologic therapy:** There is evidence that the immune system can influence the pathogenesis of melanoma. Several biologic agents have been tested in patients with metastatic melanoma and have demonstrated antitumor activity. Interferon $\alpha$ (16% RR) and Interleukine 2 (18% RR).

**Combinations of biologic agents and chemotherapy:** Exploration of combinations of biological agents and chemotherapy for treatment of melanoma is an active area of investigation. Preclinical studies on animals have suggested that combinations of recombinant cytokines or monoclonal antibodies (e.g. IL2 and Interferon $\alpha$, monoclonal antibody and IL2, tumor necrosis factor and Interferon $\gamma$) are additive or synergistic. Clinical trials of cytokines with chemotherapy have been initiated and have shown promising results (45–50% RR) with some 5 to 10% long term unmaintained remissions.

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## T cell recognition of melanoma-derived antigens: Implication for peptide based immunotherapy

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A high number of T cell-recognized epitopes expressed on melanoma cells has been recently identified. However, it is still unclear which antigen could be effective in mediating a significant anti-tumor response when used as a vaccine. Preliminary studies showed that immunization of melanoma patients with epitopes derived from proteins of the MAGE family (whose systemic immunogenicity, i.e. the ability of inducing specific CTL in peripheral blood of melanoma patients after *in vitro* culture, is apparently low) may result in significant clinical responses. On the other hand, no major tumor regression could be observed when patients were vaccinated with epitopes derived from the differentiation antigen MART-1/Melan A, an antigen that has been shown to be the most immunogenic in HLA-A2.1 melanoma patients. It is thus crucial to identify the mechanisms responsible for the failure of some antigens to mediate a significant anti-tumor response *in vivo*. One of these mechanisms has been recently identified as related to the existence of natural analogs of the MART-1 immodominant epitope in normal human proteins other than MART-1. These analogs exert a partial agonist/antagonist activity on MART-1-specific CTL, thus possibly playing a role in down modulating *in vivo* anti-melanoma CTL reactivities.

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## On the molecular genetics of malignant melanoma

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Cutaneous malignant melanoma in its hereditary form is involved in 5–10% of all melanoma cases. Genetic linkage analyses have revealed loci on chromosomes 1 and 9 as probable locations for genes responsible for the hereditary increased risk of malignant melanoma. Important steps forward were the localization of the CDKN2A gene to chromosome 9p21 and the obtained evidence of its involvement in the etiology of melanoma. CDKN2A germline mutations in American melanoma prone families have been linked to the development of the disease. In a large series of Swedish melanoma families the mutated gene was found in about 10% of the kindres. The CDKN2A gene product p16 has a regulatory effect on the cell cycle by interacting with cyclin dependent kinases. The product of a second gene, CDKN2B, on chromosome 9p21, has a similar function but no germline mutations have been observed. Both CDKN2A and CDKN2B mutations have, however, been observed in sporadic melanoma tumors. Other genes involved in the regulation of the cell cycle are at present studied. A germline mutation in the CDK4 gene have been registered in two American melanoma families. Molecular genetic studies of sporadic melanoma point at several cell cycle regulation control genes as possible targets for inherited DNA alterations predisposing for melanoma. Whether additional genes with functions in other pathways are involved in melanoma genetics remains to be determined.

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## Regional therapy for melanoma: Randomised trials

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A phase III study-EORTC 18832 and WHO Melanoma CT n°15 – on the value of prophylactic Isolated Limb Perfusion with melphalan (M-ILP) for >1.5 mm melanoma entered 832 evaluable (ev) pts from 17 centers. Median follow up is 6.4 years. There was a trend for longer DFI after ILP. The difference is significant if the pts with no ELND are separately analysed, with a high significance in the 1.5–3 mm thickness subgroup The impact of ILP was clearly on the occurrence of in transit metastases (ITM) which were reduced from 6.6% to 2.2%. There was no benefit of ILP in terms of survival.

In advanced melanoma of the limbs, ILP with melphalan combined with rTNF$\alpha$ and IFN$\gamma$ (TIM-LP) gives 100% objective responses in in-transit melanoma mets. A prospective randomized phase II study compared 32 pts who received TIM-ILP to 32 pts who received TM-ILP (without IFN$\gamma\pi$). There was an ORR and CR rate superior with TIM over TM -100% vs 91% and 78% vs 69% respectively-, but the differences are not significant.

**Conclusion:** Prophylactic M-ILP cannot be recommended as as a standard adjunct to surgery in high risk primary limb melanoma. TIM-ILP or TM-ILP is a regional therapy with very high regional response rate on melanoma in-transit mets.

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## Targeted immunotherapy: Dendritic cells to present tumor-associated antigens

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Dendritic cells (DC) are thought key regulators in immune responses. In particular DC, because of their efficient antigen uptake and processing machinery and their high expression of MHC class I and class II molecules, are well equipped to stimulate naive lymphocytes. Until recently, the extremely low abundance of DC in the circulation has hampered the study of these antigen presenting cells. Recently, several studies have demonstrated that it is possible to obtain DC from bone marrow or from peripheral blood monocytes after in vitro culture with cytokines. In particular GM-CSF and IL4 are frequently used. These immature DC can be further differentiated into mature DC using cytokines like TNF or IL-1. These cells express high levels of MHC molecules, and also CD80, CD83, and CD86. We and others were capable, using these DC as antigen presenting cells, to induce primary immune responses against melanocyte differentiation antigens. Thus we obtained several CTL from blood of healthy donors as well as from melanoma patients that recognize melanocyte differentiation antigens. These findings demonstrate that DC may be powerful immunogens and several strategies to use DC to treat cancer patients have recently been developed. These not only include the injection of DC loaded with peptides or proteins derived from tumor associated antigens, but also DC transduced with RNA or DNA encoding such proteins may be considered.

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## Surgery: Still the gold standard?

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Surgery as primary treatment for cancer of the oesophagus and gastro-oesophageal junction today is challenged by a variety of multi-modality regimens. Several groups, including our own, however have continued to advocate radical resection and extended lymphadenectomy as the primary

treatment for these tumors. From our own data and data from literature, there are mainly arguments to support this view. First extended lymphadenectomy offers better staging over clinical staging with a number of evident consequences related to non-surgical therapeutic strategies. Second wide peritumoral resection (Ro) and extended lymphadenectomy undoubtly results in better control of loco-regional recurrence rate. Third radical resection and extended lymphadenectomy seems to improve cure rate not only in stage I and II, but also in stage III provided the lymph node ratio of involved lymph nodes is less than 20%. Fourth until today no multicentric trial utilising either pre-operative chemotherapy of chemoradiotherapy has shown a clear survival advantage beyond that achieved by surgery alone.

In conclusion primary surgery especially radical surgery and extended lymphadenectomy today currently results in overall 5 years survival rates of 25–30%. These figures therefore remain the gold standard to which all other therapeutic regimens should be compared.

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## Combined treatment modalities in oesophageal cancer

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The role of combined treatment modality should be discussed in 3 clinical situations. *In early disease*, the standard treatment is a surgical resection. The median survival is around 50, 30 and 24 months respectively for stage I, IIa and IIb. Failures are equally distributed between local and distant recurrences indicating that both aspects should be addressed in the adjuvant setting. An European phase III trial that compared preoperative XRT-CT to surgery alone, included 282 evaluable patients. After 55 month follow up, the combined arm significantly increased disease free survival, local free interval and reduced cancer related death. Details results will be presented. *In locally advanced cancers*, combined XRT-CT already demonstrated a benefit in comparison with XRT alone, RTOG and EORTC studies. *In marginally resectable tumours*, XRT-CT alone instead of surgery is actually questioned in view of the poor overall prognosis.

Many ways of future developments are open: refinement of XRT to increase the dose (conformal therapy), optimisation of the treatment schemes and new drugs. Quality of life is emerging as a valuable new end point that deserve careful evaluation.

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No abstract

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## Palliative approaches in oesophageal cancer

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Palliation for patients with oesophageal cancer must be assessed not only in terms of survival duration but also in terms of quality of life. Until relatively recently surgery offered the best palliation on both these counts but with a peri operative mortality of 10%. More recently chemoradiotherapy has provided long term survival (range 12–30 months) without significant dysphagia and with no mortality to date in patients unsuitable for operation.

Laser and intraluminal radiotherapy are of limited effectiveness with a mean survival of 8.5 months. In our experience intubation either with rigid or expandable stents gives poor palliation with survival limited to 2–4 months, significant complications from tube slippage and obstruction and a peri operative mortality of 2%.

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## Molecular evolution of the esophagitis metaplasiaadenocarcinoma sequence (EMAS): Paradigms and paradoxs for cancer biology

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Adenocarinoma of the oesophagus has been increasing in the developed countries over the last three decades and probably reflects an increased incidence of its recognized Precursor lesion Barrett's metaplasia.

The real challenge for the molecular oncologist has been to explain how the processes of deregulated proliferation and cell survival interact with the early invasive phenotype. In recent scientific articles this is becoming clearer. Unfortunately the majority of precursor lesions and carinoma in-situ remain undiagnosed and when invasive neoplasia develops the tumour is associated with very poor prognosis. The improved understanding of the genetics of the Barrett's metaplasia to adenocarcinoma sequence will allow improved diagnosis, prognostic evaluation and therapeutic intervention. This review focuses on intriguing recent developments in the molecular and cell biology over the last 5 years in particular with regard to the biological heterogeneity of premalignant clones and their genetic mutations and alterations in protein processing and expression of mitogens and adhesion molecules which allows these clones to progress to invasion.

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## Brachytherapy in oesophageal cancer the radical role

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HDR Brachytherapy offers a simple, inexpensive and effective intervention for the palliation of oesophagus Cancer.

Does it have a radical role?

- to relieve obstruction and improve nutrition prior to surgery.
- in combination with pre-operative chemotherapy.
- in combination with external beam to offer a boost.
- as a form of conformal therapy.

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No abstract

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## PDQ: A comprehensive cancer information database – The U.S. experience

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Useful access to information concerning the diagnosis and management of oncologic conditions requires immediacy and accuracy. The National Cancer Institute of the USA has established a peer-reviewed process of cancer information access for patients and medical personnel. Known as PDQ, this system allows access to three large databases: clinical trials summaries, physician and organization directories, and state-of-the-art statements (SOAS) on treatment, supportive care and cancer screening guidelines. The SOAS are maintained and edited monthly, and are supported by editorial boards, which provide ongoing peer review of existing statements and of current literature. Each SOAS is available in a format primarily designed for professionals, but is also converted into a statement more easily accessible to the layperson. To further support the SOAS, a large external board of reviewers from the US and from abroad also examine the database on an ongoing basis. Improvements to PDQ anticipated over the next few years include: increasing access through new technologies, improvements in access to clinical trials information, integration of drug information from other databases, communication with other cancer information services, and increased utilization of levels of evidence in treatment and screening recommendations.

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## The start project: A European, evidence-based, state of the art instrument for clinical oncology

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The START project is a European multinational effort aimed at providing state-of-the-art knowledge on cancer treatment. It was launched by the *European School of Oncology* and currently involves more than 170 authors and reviewers from most European countries. The objective of the project is to provide a concise, regulary updated database on state-of-the-art treatment of malignant tumours. All neoplastic diseases will be included, as well as important topics of cancer care (e.g., pain therapy, practical pharmacology, etc.). Each chapter is drafted on a multidisciplinary basis (generally by a surgical oncologist, a medical oncologist, and a radiation oncologist), reedited by the Editorial Board (including a statistician), and reviewed by an internal peer-reviewer and by the Advisory Board. Critical