taining regimens compared with pts who were treated with surgery alone (P = 0.8). Although the results of this meta-analysis suggest that postoperative cisplatin CT regimens may result in a slight survival improvement, adjuvant CT in NSCLC cannot be considered a standard therapy and it is important that large, carefully conducted randomized trials be performed in this group of pts. Four such randomized trials are being conducted in Europe. One of them, the ALPI trial recently completed its accrual with more than 1,200 pts. The IALT, ANITA and MRC trials are till ongoing. The results of such trials are eagerly awaited and it is hoped that, once the value of postoperative CT is well ascertained, future developments can improve further the results of combined treatment. In such direction the recently reported results of PORT meta-analysis evaluating the role of RT are of great contribution in selecting the proper population for future studies. In fact, only patients with pN2 disease seem to have a beneficial effect in terms of survival, especially if they have a good PS, while RT is not justified in NoN1 patients. The optimal integration of CT and RT when both therapies are indicated represent another goal for future research.

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Induction treatments in marginally operable non-small cell lung cancer

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Patients (pts) with marginally operable non-small cell lung cancer (NSCLC) have a poor 5-year survival when treated with surgery alone. To improve the outcome of these pts, several authors have evaluated the feasibility and the effectiveness of induction chemotherapy (CT), and numerous phase II studies have reported promising results in terms of response and resectability. Three randomized trials evaluated the role of primary CT in operable NSCLC. The first, (R. Rosell et al), used three courses of CDDP, IFO, MMC (MIP regimen) and was stopped early after inclusion of 60 pts due to a significant improvement of survival in the neoadjuvant CT arm compared to the control arm (median survival of 26 months versus 8 months, $p < 0.001$). Both arms received post operative radiation therapy (RT). In the MD Anderson Study (J. Roth et al), three cycles of neoadjuvant CTX, VP 16, and CDDP followed by surgery were compared with surgery alone. RT was not a part of either treatment regimen. Sixty patients were randomized and median survival was 64 months in the neoadjuvant arm compared to 11 months in the control arm ($p < 0.008$). A recent follow-up confirmed these results. These two trials have shown encouraging results but the groups were small and populations heterogeneous. More recently, Depierre completed a phase III randomised trial comparing induction CT (MIP) followed by surgery to surgery alone in 375 patients with operable NSCLC. No significant benefit was observed in this trial with induction CT. The addition of preoperative concomitant RT to CT has also been evaluated in some phase II trials with encouraging results, and several studies have been recently initiated.

In conclusion, it is still unclear whether preoperative CT ± RT provide a significant and substantial survival advantage in marginally operable NSCLC. Further studies are needed to clarify the exact role of this therapeutic strategy.

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Radio-chemotherapy for stage III disease: From theory to practice

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Locally advanced non-small cell lung cancer (NSCL) still represents a challenge. Indeed, a combined approach including chemotherapy (CT) and radiotherapy (RT) has let to some slight improvements for some subsets of patients (i.e. good performance status, no weight loss...) but this was mainly achieved by a reduction of distant metastasis when a sequential approach was used; local control after RT remains dismal: less than 20% even after 65 Gy. Several drugs show great radiosensitizing properties both in vitro and in vivo and some results in phase II trials are quite promizing suggesting that a concurrent approach may be more effecient but with an increase in acute toxicity including acute esophagitis. During the last years, some large phase III trials have been launched to explore this approach. How to integrate those drugs with the new developments in the field of RT (conformal RT, modifications of the fractionation) is a major area for an intensive research but survival must remain the main objective with acute and late toxicities and pattern of failure as secondary endpoints. The latter may be only helpful to define new strategies including the place of surgery, a more useful staging system, the patient selection criteria for an aggressive approach or only to consider palliation and quality of life..

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Oncogenes and the cell cycle: Targets for modifying radiosensitivity

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Our laboratories have shown that the ras oncogene expression causes tumors to become increasingly resistant to radiation. The expression of the ras oncogene in tumor cells both renders them resistant to apoptosis and allows a prolongation of the G2 delay. There are three major goals relating to this work currently being pursued and which will be discussed, 1) to develop methods of radiosensitizing tumors that have ras mutations, 2) to determine which of the ras signaling pathways leads to alterations in radiosensitivity and 3) to understand the mechanisms underlying the G2 delay induced by radiation.

Toward the first goal we have shown that the use of farnesyl-transferase inhibitors, pharmacological agents that block activity of ras, allows tumors to be radiosensitized. These experiments have shown that treatment of tumors with ras mutations, but not those with wild type ras leads to increased radiosensitivity and increased susceptibility to apoptosis. This work has now led to a phase 1 clinical trial using these agents in patients with pancreatic cancer, lung cancer and cancer of the head and neck. The outline of this trial will be discussed.

Ras is known to signal through a variety of pathways including raf, PI3 kinase, rac and rho. This is a major focus of the lab because identification of the pathways that can lead to radioresistance could potentially allow the identification of targets that could be used for radiosensitization clinically. The current view of the invovlement of these downstream pathways will be discussed.

Lastly, the laboratory is investigating the effect of the G2 delay on radiosensitivity. Radiation causes cells to delay in G2 and there is suggestive evidence that this delay is important for radiation survival. We are attempting to characterize the G2 delay in order determine whether it is directly involved in radiation survival or control of apoptosis. We will discuss the role of cyclin expression, cdk activation and nuclear localization of the phenomenon of radiation-induced G2 delay.

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DNA damage-dependent checkpoints in yeasts and human cells

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The DNA damage-dependent checkpoint pathway is believed to be of critical importance to cancer as it is involved in the maintenance of genetic stability and, in human cells, mutation of components of this pathway result in cancer predisposition. In addition to the use of yeast model systems to study this pathway we have identified and are studying human homologues of yeast genes with roles in this pathway.

In yeast the DNA damage-dependent checkpoint pathway is composed of two upstream branches both of which either sense DNA damage or interact with specific DNA damage sensors. This information is transduced to the downstream biological consequences of checkpoint pathway activation: cell cycle arrest and transcriptional induction of a regulon of genes with roles in DNA repair. We have biochemically analysed two of the components of the yeast pathway. Rad9 is phosphorylated during cell cycle progression and hyperphosphorylated after DNA damage. Rad24 has been purified to homogeneity and interacting proteins identified by mass spectroscopy.

Expression of the human homologue *(HRAD1)* of the fission yeast checkpoint gene *rad1*$^+$ in *rad1* mutant fission yeast cells partially rescues the G2/M checkpoint defect of these cells. The hRad1 protein is overproduced in testis and some human cancer cell lines and interacts with meiotic prophase chromosomes at both synapsed and ansynapsed regions. Thus hRad1 interacts with chromosomes at sites where double strand breaks are present or being processed.