

# Pancreatic Cancer

## Experimental and Clinical Studies

AKADEMISK AVHANDLING

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Avhandlingen baseras på följande delarbeten:

- I. Callum M. Sloss, Fang Wang, Rong Liu, Lijun Xia, Michael Houston, David Ljungman, Michael A. Palladino & James C. Cusack, Jr. *Proteasome Inhibition Activates Epidermal Growth Factor Receptor (EGFR) and EGFR- Independent Mitogenic Kinase Signaling Pathways in Pancreatic Cancer Cells*. *Clinical Cancer Research* 2008 Aug; 14(16): 5116-5123.
- II. David Ljungman, Kent Lundholm & Anders Hyltander. *Cost-Utility Estimation of Surgical Treatment of Pancreatic Carcinoma Aimed at Cure*. *World Journal of Surgery* 2011 Mar; 35(3):662-670.
- III. David Ljungman, Anders Hyltander & Kent Lundholm. *Cost-Utility Estimations of Palliative Care in Patients with Pancreatic Adenocarcinoma; a Retrospective Analysis*. *World Journal of Surgery* 2013 Aug;37(8):1883-91.
- IV. Annika Gustavsson Asting, David Ljungman, Zilvinas Dambrauskas, Britt-Marie Iresjö, Anders Hyltander, Peter Naredi & Kent Lundholm. *Sequence Alterations in Tumor DNA as Related to Short Postoperative Survival in Patients Resected for Pancreatic Carcinoma Aimed at Cure*. Manuscript.



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# Abstract

## Pancreatic Cancer – Experimental and Clinical Studies

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**Background** Pancreatic cancer is one of the most lethal of known cancers and the only treatment with possibility of cure is surgery. The costs associated with treatment of pancreatic cancer are reputedly high, both in terms of morbidity and financially. To reinforce decision making there is a need to assess the costs and benefits of current treatment. Furthermore, the incitements to develop therapeutic alternatives and biologically characterize individual tumors are considerable.

**Methods** Evaluation of effects of proteasome inhibition on intracellular signaling systems using *in vitro* and *in vivo* experiments. Estimation of achieved utilities and direct healthcare costs based on a clinical cohort. Assessment of prognostic significance of structural genomic aberrations using comparative genomic hybridization and single nucleotide polymorphism analysis on resected tumor tissue.

**Results** Proteasome inhibition activated an antiapoptotic and mitogenic therapy resistance response in several mediators (EGFR, JNK, ERK and PI3K/Akt) and the inhibition of Akt and JNK increased the tumoricidal effect of proteasome inhibitors. The activation was EGFR independent and the increased cell death was not NF- $\kappa$ B mediated.

Patients undergoing resections with curative aim and patients receiving palliative care both experienced decreased health related quality of life in all SF-36 dimensions at diagnosis, without apparent improvement over time. The cost of treatment for patients undergoing surgery was two times the cost for the palliative patients (€50,950 vs. €23,701). Interestingly, already after one year the achieved QALY was twice as large in the resection group (0.48 vs. 0.20) resulting in cost per QALY neutralization between groups.

DNA copy number alterations were seen in 2p11.2, 3q24, 8p11.22, 14q11.2 and 22q11.21. No convincing specific aberrations of prognostic value were found. Short survival was however responsible for 67% of total copy number variation and associated with significantly more amplifications, possibly related to alterations in chromosome 2, 11 and 21.

**Conclusions** Proteasome inhibition is a promising adjunct in horizontal targeted therapy regimens and the effect may be potentiated by simultaneous inhibition of signaling systems. Costs for pancreatic cancer surgery are comparable to other major healthcare interventions and long term survival in a few is effectively increasing cost-effectiveness on patient group basis. DNA from patients with poor prognosis contains more amplifications and seems to be generally more degenerated possibly indicating a greater genomic instability. The pancreatic cancer mutational profile is displaying vast inter-individual heterogeneity and most mutations are probably passengers.

**Keywords:** Pancreatic Neoplasms; Proteasome Inhibitors; Apoptosis; Intracellular Signaling Peptides and Proteins; Epidermal Growth Factor Receptor; Pancreaticoduodenectomy; Cost and Cost Analysis; Quality-Adjusted Life Years; DNA Copy Number Variations; Comparative Genomic Hybridization