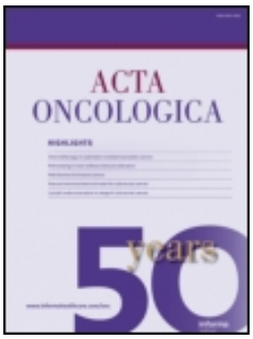

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EDITORIAL

Any progress in pancreatic cancer? Well, but progress for Acta Oncologica

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In this issue of Acta Oncologica, Doctor Simianu et al. [1] describe the progress made in pancreatic cancer. The article is based upon an Acta Oncologica Lecture held by Doctor Lillemoe at the XL Nordic Meeting of Gastroenterology in 2009. The Acta Oncologica Foundation has in many years supported Acta Oncologica Lectures presented by invited lecturers at different scientific meetings held in one of the Nordic countries. This support of exchange of scientific information continues, and any organiser can ask for permission to arrange such a lecture [2]. All costs for the lecturer will then be reimbursed by the Foundation. The intention is to publish an article based upon the lecture, to further spread the scientific information. The article by Simianu is the latest of a long series of successful papers, most recently [3–6].

Pancreatic cancer caries a decimal prognosis, and most scientists would immediately question whether any progress has been made. The authors of the article conclude that "the modern era has witnessed great progress, with gradually evolving attitudes towards the surgical intervention. The role of the surgeon has been reinforced, with greatly reduced perioperative mortality, although morbidity and mortality from the disease remain high". Some progress has also been seen in the understanding of the biology behind PC, in clinical staging and in palliation of the patients. The extensive desmoplasia seen in most pancreatic cancers [7] can be one reason for the aggressive behaviour of the disease and its refractoriness towards present therapies [8]. Not only the tumour cells but also cells and components of the stroma may be relevant targets for novel treatments. The future importance of targeted multimodality treatments is emphasised in the article [1].

Progress made in medical and radiation oncology alone or complementary to surgery has been very limited in pancreatic cancer. Somewhat surprisingly, postoperative chemotherapy with 5-fluorouracil/leucovorin or gemcitabine after surgical resection has diminished the risk of recurrence and as a consequence improved 5-year survival [9,10], in spite of their low activity in metastatic disease. The absolute gains are not large, but sufficient for gemcitabine to be incorporated into clinical routines at many centres [11]. In metastatic disease, the gains are also limited, but again considered sufficient for routine use by most clinical oncologists. As described [1], gemcitabine established itself as reference treatment after a phase III study [12] where it was slightly superior compared with 5-fluorouracil given as a 30 minute infusion, possibly the least effective way to give 5-fluorouracil [13]. Since then, we have repeatedly witnessed one unsuccessful large phase III trial after the other [14]. The addition of new targeted agents has also failed to show superiority with the possible exception of the epithelial growth factor receptor (EGFR) inhibitor erlotinib. In a large multicentre study, it conferred a very modest survival prolongation when added to gemcitabine (median survival gain about 10 days, hazard ratio 0.82 [0.69–0.99]) [15]. This gain is clinically also too small, at least in my and others views [11], although it is likely that a small subset of patients gain from EGFR inhibition. For the future development, it is necessary to find markers identifying those individuals.

Need for new trial designs

The interpretation of basic and clinical knowledge in the design of clinical trials in pancreatic cancer was discussed in a National Cancer Institute (NCI) planning meeting that resulted in a consensus report [16]. Emphasis was placed on the enhancement of research

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to identify and validate the relevant targets and molecular pathways in pancreatic cancer, cancer stem cells and the microenvironment. Emphasis was also placed on developing predictive markers to assist selection of patient subsets. The many negative phase III trials in pancreatic cancer prompted the meeting to state that phase III clinical trials should be implemented only if there is a meaningful clinical signal of efficacy and safety in the phase II setting. Many small steps may become one large leap, but there have been too many attempts driven by the drug industry to statistically significantly show the small steps. Please read also two very well written Comments and Controversies about the future of clinical trials in oncology [17,18]. Although patient advocates and many investigators indicated the feasibility of performing studies that do not include gemcitabine as initial therapy, i.e. to perform so called window-of-opportunity trials, or short window-trial, this was not included in the final recommendations of the Consensus report [16]. In a window-trial, the experimental treatment is given before an established treatment with known clinical activity. Window-trials have been successfully applied in paediatric cancer, but rarely used in adult oncology. The window design has the advantage of exploration of a novel treatment without the negative influence of previous treatments and often a heavy tumour burden in patients failing after multiple lines of chemotherapy. It requires strict criteria and close monitoring of the patients in order not to sacrifice overall survival. An attempt to a "window-trial" in advanced pancreatic cancer was already made in 1998 [19]. In a NCI sponsored randomised phase III trial, standard gemcitabine was compared with an experimental complementary medicine treatment including pancreatic proteolytic enzymes. Because most eligible patients refused random assignment, the trial was changed in 2001 to a controlled, observational study. In 2005 the study was closed to accrual. Of 55 enrolled patients, 23 received chemotherapy and 32 experimental therapy. Clinical characteristics were similar between the two groups. Overall survival was longer in the chemotherapy group (14 months, much longer than seen in the chemotherapy trials, about 6–7 months, than in the experimental group, 4 months, being similar to what was seen in best supportive care trials) [13]. We must clearly look for new targets, but also for alternative trial designs [17,18], and a window design is then an attractive alternative, but it requires a very strong preclinical rationale. In metastatic colorectal cancer we recently completed a window trial using a novel inhibitor of protein kinase C (PKC-beta, enzastaurin) [20]. Although it was difficult to rapidly enrol many patients, the trial showed that a window design is feasible and that overall survival is not compromised [21]. Progress in pancreatic cancer has been seen [1], but it has been extremely slow and still only incremental.

Progress for Acta Oncologica

Coming back to the Acta Oncologica Lecture mentioned above, the Foundation has taken several other steps that have successfully resulted in great progress for Acta Oncologica. The impact factor increased to a new top level (2.739 in 2008). The number of submitted manuscripts has increased from below 200 some years ago to about 600 during the past two years. This has resulted in a considerably higher rejection rate (about 70% in 2009) but also in the publication of an increasing number of high quality papers, witnessed by more citations and downloadings. Acta Oncologica has during the past few years further supported several Acta Oncologica and other symposia and we have had the fortune to be able to publish many good articles filling whole issues from these meetings. During 2009, two special issues were published, in issue 2 papers from the Nordic Association of Clinical Physics meeting [22] and in issue 5 from The Nordic Occupational Cancer (NOCCA) symposium [23]. Due to very favourable experience of publishing papers from scientific meetings, this will continue during 2010 and on. You may already have seen some of them [24–26] from the State of Science Conference in Cancer Care – Identification of frontline research topics.

In 2008, we had the pleasure to welcome the first Acta Oncologica Research Fellow, Associate Professor Beatrice Melin, Umeå, Sweden [27]. Last year we had the pleasure to welcome a second holder of a five year research fellow post, Associate professor Julie Gehl, Herlev, Copenhagen, Denmark working with a project "Electroporation for drug and gene delivery in the treatment of cancer".

As I expressed in an editorial previously [27], I hope you continue to value the papers accepted for publication in Acta Oncologica. Papers coming from the special activities continue to be the most downloaded and cited articles, but also several other, spontaneously submitted articles are frequently read and cited. Unfortunately, but far from unique for Acta Oncologica, many papers are never cited.

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