# Polarographic $pO_2$ Measurements of Intra-abdominal Adenocarcinoma in Connection with Intraoperative Radiotherapy Before and After Change of Oxygen Concentration of Anaesthetic Gases

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In well-oxygenated cells the response to commonly used ionizing radiation is enhanced compared with that in cells irradiated under hypoxic conditions. The ratio of doses needed to eradicate hypoxic cells as compared to well-oxygenated cells is called the oxygen enhancement ratio (OER). This ratio is between 2 and 3 for sparsely ionizing radiation such as gamma-, x-rays and electrons commonly used in radiotherapy; the higher the dose per fraction, the higher the OER (1). For practical reasons only high, single doses are given in connection with intraoperative radiotherapy (IORT), which is used at hundreds of centers world-wide. The main tumour locations where IORT has been used are intraperitoneal or intrapelvic and frequent diagnoses are adenocarcinoma of the pancreas, common bile duct, gallbladder and rectum. The IORT dose given is in the order of 15–20 Gy and is usually a conformal boost complementary to external fractionated radiotherapy given either before or after. The fractionated therapy is usually given with doses of 2 Gy per day, 5 days per week, up to a target dose of about 40 Gy. This supplementary fractionated radiotherapy may, besides increasing the total tumour dose, also allow for some reoxygenation of tumour cells. IORT is used both after macroscopically radical surgical extirpation of the tumour as well as in cases of unresectability. When IORT has been part of a combined therapy, the results have been promising; for example in the treatment of primary unresectable adenocarcinoma of the rectum (2). So far, there has been only one randomized trial where a satisfactory number of patients have been included (3). This study shows a significant difference in survival in favour of IORT as a supplement to surgery in locally advanced gastric cancer. Owing to practical and ethical considerations, it has been impossible to accrue satisfactory numbers of patients for several prospective randomized trials that have been initiated. (4).

In the case of unresectable cancer, tumours of the pancreas or the gallbladder, the results are not convincing either with respect to survival or local tumour response despite the very high total irradiation doses to the tumours. The lack of gain with respect to survival is to a large extent dependent on occult dissemination when surgery is performed. Usually there is no detectable local tumour regression, indicating low radiosensitivity of unresectable tumours. Possibly, this lack of radiosensitivity to a large extent is due to the hypoxia of the adenocarcinoma of these organs.

In order to investigate the oxygen partial pressure ($pO_2$) distribution of unresectable tumours, polarographic needle measurements were performed in three consecutive patients undergoing IORT. The purpose was also to investigate whether $pO_2$ of the tumours increases a few minutes after a change in the anaesthetic gas mixture towards 95% oxygen. The patients were kept normocapnic during the study.

Three consecutive patients, all with adenocarcinoma verified by cytology during laparotomy, were studied. The tumours were unresectable because of local growth into abutting unresectable vital organs, but no signs of dissemination were found. The tumours originated in the pancreas (patient 1), the common bile duct (patient 2) and the gall bladder (patient 3), and had diameters of approximately 4, 3 and 4 cm, respectively.

Tumour oxygen partial pressure was measured using a computerized $pO_2$ histograph with a polarographic needle electrode (Model 6650, Eppendorf, Hamburg, Germany) as described elsewhere (5, 6). Initially, the oxygen electrode was allowed a few minutes of adaptation to the tissue environment. Thereafter, measurements were made over predetermined distances (tracks) according to tumour size and accessibility. At least two parallel tracks were made resulting in an average collection of 38 measurement points (range 18 to 63) within the individual tumours. The oxygen needle moved automatically in a stepwise pattern in order to minimize tissue compression artefacts: 1 mm forward, followed by a 0.3 mm retraction, giving a net step length of 0.7 mm between each measurement point. Before and after each series of measurements the fine-needle probe was calibrated using sterile buffered 0.9% NaCl solution at pH 7.8, equilibrated alternately with atmospheric air and 100% nitrogen at room temperature. The measured values were corrected for air pressure and temperature differences between the calibration vessel and the tumour.

After an initial phase of general anaesthesia, the concentration of the inhalation gases was kept at the commonly used levels of about 30% $O_2$, 66% $N_2O$, and 4% desflurane. When the surgeon uncovered the tumour, some 40–60 min after the initial phase, a first measurement series of $pO_2$ was performed. A change in the inhalation gas mixture was then instituted so that the oxygen content was now about 95%, $N_2O$ at 0%, while desflurane was kept unchanged. After an 8-min breathing time period, when by monitoring the expired gases no $N_2O$ was left indicating a steady state, a further set of $pO_2$ readings were acquired.

After the second $pO_2$ measurements the surgical procedure continued and a suitable electron collimator (circular plastic treatment cone) was placed just proximal to the target volume and fixed to the operating table through a frame. The patient was then moved, together with the anaesthetic stand, through an airlock to the next-door treatment room equipped with a linear accelerator (Phillips/Elekta SL25) by which electrons up to 22 MeV can be delivered. The design concept and the dosimetric characteristics of the soft-docking system used for IORT have been described previously by Björk et al. (7). The accuracy of the alignment of the central axis of the treatment machine and the length axis of the treatment cone in the patient was guaranteed using a remote-controlled operating table and a TV system directed via a mirror and a two-level sight. The electron energy was chosen so that the 85% isodose covered the planned target volume. Some 8 min before the IORT dose was given, the inhalation gases were once more changed to the high oxygen mixture which was used before the second series of $pO_2$ measurements and this gas breathing continued during treatment.

The data from the patients are summarized in the Table. As proposed by Ebbesen et al. (8), the oxygen partial pressures are expressed in SI units, i.e. kiloPascal. The median $pO_2$ values were chosen to be the measure of tumour oxygenation before and during high oxygen gas mixture breathing. The percentages for values $\leq 0.667$ kPa (5 mmHg) and $\leq 1.333$ kPa (10 mmHg) are also shown. All three tumours initially had a relatively low oxygen tension. After high oxygen breathing, a rise in median $pO_2$ and a decreasing number of hypoxic measurements were observed in all tumours. In patient 2, measurements were also made in apparently normal liver tissue, where the median $pO_2$ was almost unchanged between the measurements before and after the change in oxygen content of the breathing gases. Analysis of partial pressures of arterial blood showed a more than doubled increase in oxygen content during high oxygen breathing while the $pCO_2$ was almost unchanged.

The correlation between relative radiosensitivity and oxygen tension is well documented (9). Those investigations were based on single fraction studies on the effect of radiation of low linear energy transfer and should then be applicable when large single electron doses are given in connection with IORT. Since hypoxia is not to be accounted for in normal tissues that might be included in the IORT treatment field, any increase in oxygen pressure above some 4 kPa caused by the extra supply of oxygen should have no influence on their radiosensitivity. Based on the data given by Hall (9) and the observed increase of median $pO_2$ of the three tumours shown in the Table, an estimated increase of the relative radiosensitivity would be as follows: (1) the pancreatic tumour, 1.80 to 2.76 (53%); (2) the common bile duct tumour, 2.46 to 2.88 (17%); and (3) the gallbladder tumour, 2.16 to 2.28 (5.6%).

The optimal time for increasing the oxygen pressure of tumours after a change of $O_2$ content in the breathing gas is not clear. However, Falk et al. (10) found an almost immediate increase of the median oxygen pressure in 12 out of 17 tumours, mostly breast cancer and other forms of readily accessible tumours. The maximum increase was measured in some of the patients after about 10 min of breathing carbogen (95% $O_2$ and 5% $CO_2$). A decline in tumour oxygen tension was registered at about 15 min after onset of carbogen breathing. Whether or not these data are applicable to patients under general anaesthesia is not certain, but it seems advisable to introduce a change of breathing gases, so that a higher $pO_2$ of the tumour is reached just before giving the IORT dose. The duration of IORT radiation time is usually in the order of 15 min.

No unexpected secondary effects were found during and after therapy. One patient (1) died as a result of disease dissemination. No autopsy was performed. Patient 2, a 41-year-old man, is well 15 months after IORT and a recent MRI investigation showed a more than 50% regression of the tumour. Patient 3, a 55-year-old woman, is without severe symptoms and has stable disease according to a CT investigation performed 13 months after IORT.

Admittedly, the number of patients included in this study is small. As far as we know there is no published data on $pO_2$ of adenocarcinoma of the types we have investigated. It is, however, reasonable to assume that most sizeable adenocarcinomas are to some extent hypoxic (6, 10, 11) and that the administration of a high concentration of oxygen during IORT may improve the local response. Since no harm to the patients undergoing these changes of breathing gases during general anaesthesia has been shown or is likely, it is therefore advisable to introduce the method to more patients undergoing IORT for further evaluation of the expected benefit.

**Table 1**

*Effect of changing the oxygen concentration of anaesthetic gases on the tumour $pO_2$ of three consecutive patients undergoing IORT*

| Site of tumour (Patient no.) | Median $pO_2$ (kPa) | | (a): $pO_2$ values $\leq 0.667$ kPa (%)<br>(b): $pO_2$ values $\leq 1.333$ kPa (%) | |
|---|---|---|---|---|
| | Before[1] | After[2] | Before[1] (a)/(b) | After[2](a)/(b) |
| Pancreas (1) | 0.28 | 2.41 | 98/98 | 16/24 |
| Common bile duct (2) | 1.07 | 3.71 | 0/72 | 0/6 |
| Gallbladder (3) | 0.55 | 0.73 | 95/100 | 44/88 |

[1] Common anaesthetic gas mixture breathing (30% $O_2$).

[2] After about 8 min of high oxygen breathing (95% $O_2$).

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