Intraoperative hyperthermia in conjunction with multi-schedule chemotherapy (pre-, intra- and post-operative), by-pass surgery, and post-operative radiotherapy for the management of unresectable pancreatic adenocarcinoma

V. E. KOULOULIAS††*, J. R. KOUVARIS†, K. S. NIKITA‡‡, B. C. GOLEMATIS§, N. K. UZUNOGLU‡‡, K. MYSTAKIDOU†, C. PAPAVASILIOU† and L. VLAHOS†

† Department of Radiotherapy, Medical School, University of Athens, Aretaieion Hospital, 76 Vas. Sophias Avenue, 11528 Athens, Greece
‡ Institute of Communication and Computer Systems Department of Electrical and Computer Engineering, National Technical University of Athens, 9 Iroon Polytechniou Street, Zografos 15773, Athens, Greece
§ 1st Department of Propaedeutic Surgery, Medical School, University of Athens, Hippocration Hospital, 114 Vas. Sophias Avenue, 11527 Athens, Greece

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The aim of this study was to evaluate the potential role of intraoperative hyperthermia (IOHT) in the management of stage IV pancreatic adenocarcinoma. Twenty-seven patients (group A) received pre-operative chemotherapy (5-FU), by-pass surgery with intraoperative bolus infusion of 5-FU and post-operatively multi-agent chemotherapy plus sandostatin and external beam irradiation (45 Gy, 25 fractions, 5 days a week). In a non-randomized way, 10 patients (group B) received an additional single session of IOHT (43–45°C, 1 h) performed directly on the tumour using a waveguide applicator (433 MHz) with interstitial measurements of temperature measured. A brief instrument was developed for evaluating patients' quality of life. No progressive disease (PD) was noticed in group B vs 11% (3/27) of PD in group A. There was also a significant increase of overall survival (OS) in group B vs A patients (p < 0.029, log-rank test). Moreover, there was a significant improvement for group B vs A patients regarding Karnofsky performance status (p < 0.001, Mann-Whitney test), pain score (p < 0.001, Mann-Whitney test) and quality of life score (p = 0.031, Mann-Whitney test). A significant correlation was noticed between OS and thermal parameters such as average T_min (p = 0.043), average T_max (p = 0.027) and cumulative minutes T90 ≥ 44°C (p < 0.001). Combined IOHT with chemotherapy (pre-, intra- and post-operative) and external beam post-operative radiotherapy seem to have a potential benefit in the management of unresectable adenocarcinoma of the pancreas, concerning local response, OS and quality of life. Further clinical studies to evaluate the benefit of IOHT suggested in this study are warranted.

Key words: Unresectable pancreatic adenocarcinoma, intraoperative hyperthermia, radiotherapy with pre-operative plus intra-operative regional plus post-operative chemotherapy, survival analysis, palliation, quality of life.

1. Introduction

Pancreatic cancer is invariably diagnosed in the advanced stage because of the lack of specific symptoms or signs. Nearly 50% of the tumours are classified as locally advanced, with a median survival not excited at 5 months. Over the last decade, the curative modality for adenocarcinoma of the pancreas remains dismal.

* To whom correspondence should be addressed. e-mail: vkouloul@cc.ece.ntua.gr
Approximately 40% of patients with pancreatic carcinoma will be explored and undergo some type of palliative bypass procedure, and only 15% will be resected for cure. Palliative surgery does not affect survival, since the median overall survival is limited to 4.5–12 months and does little to ameliorate the pain and cachexia frequently associated with this disease.

It is well known that 5-FU does improve irradiation as a radiosensitizer for pancreatic carcinoma. Although there are several reported studies concerning the improvement of local control and a significant effect on pain relief after external beam of radiotherapy, there is only a slight benefit to survival. Intra-operative radiotherapy mainly results in pain relief without affecting tumour regression or overall survival. Many trials with single-drug or multi-agent chemotherapy have been published over the years, but without any significant or major survival benefit. However, 5-FU has a well-documented efficacy in pancreatic cancer, while gemcitabine seems to improve further the median survival up to 1 or 2 months. New agents and new therapeutic modalities have been applied in order to improve therapy of this disease. Several studies focusing on the anticancer effects of octreotide and related somatostatin analogues reported promising results concerning the local control and pain relief as well, especially in pancreatic carcinomas. Surgical procedure, radiation therapy technique, type of chemotherapy and hormonal therapy, or the combinations thereof, do not have a definite clinical benefit in terms of a significant improvement in survival; the local control of advanced disease, the liver metastases and the peritoneal seeding remain the major problems.

Primary reports of intra-operative hyperthermia suggest promising results concerning pain-relief. Local IOHT has already been used, with quite promising results, without systemic toxicity. Attempting to improve local control and patient’s quality of life, one applied a new treatment modality using the combination of a single session local IOHT with intra-operative (intra-arterial) chemotherapy. In pancreatic tumours, the addition of hyperthermia to a multimodality treatment (intra-operative radiation therapy, post-operative irradiation and chemotherapy) improves pain relief, local tumour control and survival.

The concept of combining hyperthermia with chemotherapy for pancreatic tumours was based on the well-known cell killing properties of hyperthermia and on its synergistic effects with many chemotherapeutic drugs. 5-fluorouracil has been chosen in the present approach due to its synergetic interaction with hyperthermia.

The aim of this study was to evaluate the possible benefit of multimodality treatment constituted by intra-operative hyperthermia, post-operative radiotherapy and chemotherapy (pre-, intra- and post-operative) in local control, overall survival, pain relief and quality of life of patients with unresectable pancreatic carcinoma.

2. Patients and methods

2.1. Patients and study design

From December 1991 through August 1996, 37 patients with TNM-AJCC stage IVA or IVB, (American Joint Committee on Cancer) adenocarcinoma of the pancreas were administered in Hippokration Hospital at the 1st Department of Propaedeutic Surgery of Medical School of University of Athens, for treatment. The patient’s age ranged from 37–71 years (median 62 years) and the male-to-female ratio was 20:17. The tumour volume ranged from 10–70 cm$^3$. In all cases, the primary malignant neoplasm was a moderately or poorly differentiated adenocarci-
following criteria for entering the trial: Karnofsky Performance Status > 50; WBC ≥ 3500 μl⁻¹; platelet ≥ 100 000 μl⁻¹; hemoglobin ≥ 9.5 gm/dl; total bilirubin ≤ 2.0 mg/dl; aspartate transaminase and alanine aminotransferase less than three times the upper limit of normal; serum creatinine concentration ≤ 1.5 mg/dl.

Patients’ pre-treatment characteristics for group A and B, according to clinical (performance status, pain score and quality of life score) and radiological (computerized tomography) evaluation, are shown in table 1.

Patients were divided into two groups. The major criterion for patients receiving IOHT or not was the cardio-vascular clinical evaluation from the anaesthesiologists and cardiologists, by means of the possibility of a patient undergoing a time-consuming surgical operation constituting of accessioned 60 min of IOHT. Although it seems that patients were highly selected, the cardiovascular evaluation was not related directly to the treatment outcome; carciocvascular evaluation doesn’t seem to be a probable prognostic factor. At the beginning of the protocol, there was an attempt to randomize the trial, in order to make statistical evaluation more reliable. Unfortunately, some patients that were randomized to receive IOHT refused to undergo this treatment modality and the initial randomized design of the study collapsed. Therefore, in order to save the trial, it was decided to keep the situation as it was, not underestimating the fact that the design of the study was turned into a non-randomized prospective one. Group A constituted 27 patients who received pre-operative chemotherapy, surgery plus intra-arterial regional chemotherapy (IARC) and post-operative radiotherapy. Finally, group B constituted 10 patients treated additionally with intraoperative hyperthermia (IOHT) from January 1992 through July 1996. Patients in both groups received post-operatively sadostatin 0.1 mg/6 h for 3 days. Pre-operative chemotherapy started 96 h before surgery and was administered by continuous intravenous infusion of 1 g 5-fluorouracil for 96 h.

The inoperable stage of the disease was confirmed before surgery by CT-scans in the upper abdomen. During laparotomy, a more accurate evaluation of the tumour-invasion to neighbouring organs was carried out. Nineteen out of 27 patients in group A and six out of the 10 patients in group B had a tumour invading the great vessels (i.e. superior mesenteric artery or portal vein) or neighbouring organs (duodenum, stomach) with or without metastases to the regional lymphnodes. These

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
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<tbody>
<tr>
<td>IOHT *</td>
<td>—</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>17/10 (63/37)</td>
<td>3/7 (30/70)</td>
<td>20/17 (54/46)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>60 (44–71)</td>
<td>62 (37–70)</td>
<td>62 (37–71)</td>
</tr>
<tr>
<td>KPS &gt; 60/KPS &lt; 60 ** (%)</td>
<td>10/17 (37/63)</td>
<td>4/6 (40/60)</td>
<td>14/23 (38/62)</td>
</tr>
<tr>
<td>SHPS &lt; 6/SHPS &gt; 6† (%)</td>
<td>7/20 (26/74)</td>
<td>3/7 (30/70)</td>
<td>10/27 (27/73)</td>
</tr>
<tr>
<td>QoLMS‡ (±SD)</td>
<td>42.9 (±7.9)</td>
<td>41.9 (±8.2)</td>
<td>42.2 (±8.1)</td>
</tr>
</tbody>
</table>

* Intra-operative hyperthermia; ** Karnofsky Performance Status; † Scott-Huskisson pain scale (visual-analogue scale); ‡ Quality of life mean score.
in group A and four in group B were found to have a tumour extended directly to the large vessels, to duodenum, bile duct and peri-pancreatic tissues (mesenteric fat, mesocolon, greater and lesser omentum) with liver secondaries and multiple metastases to regional lymphnodes. These patients were staged as IVB (T4N1M1 according to TNM-AJCC). Choledochoduodenostomy for biliary bypass was performed in 34 of the 37 (91.9%) patients as palliative operation. One patient from group B and two from group A had a very large inoperable tumour extending from the head to the tail of the pancreas, with multiple liver metastases. These three patients (8.1%) underwent choledochojejunostomy, gastroenterostomy and Roux-en-Y anastomosis. All patients received sandostatin 0.1 mg/6 h post-operatively for 3 days. Patient distribution according to stage for group A and B is shown in table 2. A bolus infusion of 500 mg 5-FU was administered intra-operatively through the gastroduodenal into the splenic artery (Intra-Arterial Regional Chemotherapy, IARC). The chemotherapy drug (500 mg of 5-fluorouracil) was diluted in 100 ml of normal saline and then infused for a period of 60 min during intra-operative heating. The drug was then infused regionally according to tumour location, i.e. though the gastroduodenal into the splenic artery for tumours located in the pancreatic body/tail, into the gastroduodenal, not exceeding the joint of common-hepatic and gastroduodenal, for tumours located in the pancreatic head, by combined the two procedures when the tumour was located in the head and in the body/tail. IARC was administered simultaneously with IOHT in group B.

Post-operatively, with a median time interval of 7 days, all patients also received six sessions (every 3 weeks) of multiagent chemotherapeutic course (5-FU, doxorubicin and cisplatin). The chemotherapy schedule constituted 5-fluorouracil (5-FU) at a dose of 500 mg/m² IV on days 1 and 8, doxorubicin at a dose of 50 mg/m² on day 1 and cisplatin at a dose of 60 mg/m² on day 1. Courses were repeated every 3 weeks. The second session of 5-FU was administered at a dose of 300 mg/m²/day for 5 days, concurrently with the radiotherapy schedule. In both groups, patients received external beam post-operative irradiation with a 6 MeV linear accelerator (total dose 45 Gys in 25 fractions, 1.8 Gy per fraction, 5 days a week). Radiotherapy was administered with three fields per session (two weighted lateral and one open anterior, supine patient’s position) encompassing the pancreatic area. The dose produced to the left kidney was diminished due to a small angle in the arrangement of the two lateral fields and mainly due to a lead shield that was placed in the anterior field to eliminate the dose in the inferior pole of the organ. The radiation portals in terms of dimension were 11 × 10 cm for the anterior field and 10 × 10 cm for each of the lateral fields. The tumour volume was defined using small radiopaque clips placed at tumour-margins at the time of surgery. The post-operative irradiation was administered post-palliative-surgery with a median time interval of 33 days.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA</td>
<td>T4N0Mx</td>
<td>3/27 (11%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td></td>
<td>T4N1Mx</td>
<td>16/27 (59%)</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>IVB</td>
<td>T4N1M1</td>
<td>8/27 (30%)</td>
<td>4/10 (40%)</td>
</tr>
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</table>
the declaration of Helsinki and was approved by the ethical review board at the institution. All patients gave written informed consent before entering the study.

2.2. Intra-operative hyperthermia procedure

In group B patients, during the by-pass operation, the area of interest (cancerous...
exposed tumours was then administered. Intra-operative heating was performed using direct contact waveguide applicators. Applicators operating at 433 MHz, used for treating superficial tumours\textsuperscript{23}, were appropriately modified in order to achieve compatibility with the surgical procedure and the size of the regions to be treated. Waveguide applicators of either rectangular or circular aperture were available, the choice between them depending on the surgical field and the tumour dimensions. The specific absorption rate (SAR) patterns were measured inside well-documented phantoms\textsuperscript{24}, showing a penetration depth of nearly 3 cm\textsuperscript{23}. The effective field size in terms of 50\% SAR for the circular (diameter $= 7.5$ cm) and rectangular ($5.8 \times 2.9$ cm) applicator were 28 and 15 cm\textsuperscript{2}, respectively. The waveguide applicator was covered by sterilized nylon and its radiating aperture was placed in direct contact with the surface of the region to be heated. During IOHT session, special care was taken due to the presence of important vessels (i.e. superior mesenteric and splenic arteries) in the region of heating, in order to avoid heat damage in the endothelium of these vessels and/or unexpected cooling due to blood circulation. This was done by slightly changing the direction of the microwave-applicators, not to be oriented towards the vessels. The stomach and transverse colon were removed carefully, to be protected from thermal injuries.

Temperature was continuously measured during the whole hyperthermia session through a 15-gauge flexi-guide catheter carrying a thermocouple probe implanted into the tumour. The thermocouple probe with three measuring points measured temperature along the applicator axis, corresponding to 1, 1.8 and 2.6 cm depth from the surface of the region to be heated. Adjustments in emitted microwave power were made during treatment, in order to maintain the monitored temperature within 43–45°C for 60 min. The monitored temperature reached the target of 43°C in only 1.5–2.5 min. According to the literature, parameters associated with local control include average minimal intratumoural temperature and the temperature exceeded an index measured intratumoural temperature such as 43 or 44°C\textsuperscript{25}. It is already reported that thermal dose, defined as the cumulative minutes of monitored temperatures $T \geq \text{index}^\circ$C, is a predictive variable for local response\textsuperscript{26,27}. Thus, monitored temperatures were converted to $T_{\text{min}}$ (average minimum), $T_{\text{max}}$ (average maximum) and to cumulative minutes of 90\% of measured temperatures $T \geq 44^\circ$C (CUM MIN $T_{90} \geq 44$). Details of the hyperthermic treatment by means of thermal parameters for each patient are given in table 3.

2.3. Quality of life brief instrument (QoLBI)

The instrument was designed to be a self-assessment. The quality of life brief instrument (QoLBI) is a 10-item questionnaire, composed of three multi-item scales and a single item scale. It incorporates four scales (Activity, Health Status, Psychological state, and Overall Quality of Life). Three of the scales were presented into three optional statements to be scored 1, 2 and 3, respectively, and the patients were asked to circle the answer they felt best described their own state with regard to that item. The last scale (Overall Quality of Life) contains one item and has the form of a bi-polar numerical scale from 0–10. Each scale was presented in the self-assessment instrument by a title. The instructions and the methods to be used were explained to patients in a standard way by the researcher, who answered any questions before the completion of the instrument. Two major measurements with QoLBI were done: firstly at baseline of the combined protocol (beginning of pre-
The average of the items that contribute to the scale was assessed. A linear transformation was used in order to standardize the raw score, so that higher mean scores from 0 to 100 represent a better level of quality of life. The final quality of life score (GoLS) was obtained from the mean value of all the scales of the instrument (including the overall quality of life evaluation). The outline on the instrument is shown in the appendix.

2.4. Follow-up, endpoints

The major endpoint was overall survival measured from the time of histological diagnosis until the time of death. Follow-up was continuous, every month after surgery for 6 months and, after that, every 3 months until death. Clinical examination and CT-scans were done at every follow-up. Baseline measurements for pain-score and Karnofsky Performance Status (KPS) were taken at the beginning of pre-operative chemotherapy. The pain score was measured according to the Scott-Huskisson 0–10 visual-analogue scale\textsuperscript{28}, producing a score named Scott-Huskisson Pain Score (SHPS). Values of KPS and SHPS were also evaluated 1 month after the combined protocol. Any difference (improvement, stable or worsening) in SHPS and KPS from the baseline was evaluated, constituting two new variables termed Benefit of Karnofsky Performance Status (BKPS) and Benefit of Scott-Huskisson Pain Score (BSHPS). The mean value of the final quality of life score was also used as an endpoint regarding its improvement separately for groups A and B. Improvement or worsening for the above parameters was marked with a plus or minus sign, respectively. $T_{\text{min}}$, $T_{\text{max}}$ and cumulative minutes $T_{90} \geq 44^\circ \text{C}$ were also used as endpoints for correlation with treatment outcome. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) were also evaluated at diagnosis and post-operatively (1 month after the last session of radiotherapy, during the chemotherapy schedule).

Tumour volume response was assessed by reviewing pre- and post-combined treatment modality course CT-scans and measuring the tumour volume. A radiological response was defined as partial, since there was a $\geq 50\%$ decrease in tumour volume for a minimum of 4 weeks, with no evidence of new lesions or increases of more than $25\%$ of the lesions already noticed. Stable disease stood for a decrease of $< 25\%$ in the tumour volume. Progressive disease was defined as an increase in the

<table>
<thead>
<tr>
<th>Case</th>
<th>$T_{\text{min}}$</th>
<th>$T_{\text{max}}$</th>
<th>CUM MIN $T_{90} \geq 44^\circ \text{C}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42.4</td>
<td>44.8</td>
<td>11.0</td>
</tr>
<tr>
<td>2</td>
<td>43.1</td>
<td>44.3</td>
<td>35.0</td>
</tr>
<tr>
<td>3</td>
<td>43.2</td>
<td>44.8</td>
<td>36.0</td>
</tr>
<tr>
<td>4</td>
<td>43.3</td>
<td>45.4</td>
<td>16.0</td>
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<td>5</td>
<td>42.8</td>
<td>44.5</td>
<td>16.0</td>
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<td>44.6</td>
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<tr>
<td>7</td>
<td>42.4</td>
<td>45.1</td>
<td>13.0</td>
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<td>45.4</td>
<td>33.0</td>
</tr>
<tr>
<td>9</td>
<td>42.9</td>
<td>45.1</td>
<td>14.0</td>
</tr>
<tr>
<td>10</td>
<td>43.1</td>
<td>45.4</td>
<td>29.0</td>
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volumetrics of the pancreas, digital reconstractive radiographs (DRRs) were used and the maximum diameter of the x-, y- and z-axes were recorded. However, this was problematic due to the fuzzy anatomical region of the pancreas, as it appeared in the CTs. For this reason, three independent experts in computerized tomographic radiology reviewed the DRRs in correlation with the cross-sectional CT-slices. The final values were derived by the mean value of the three individual measurements.

2.5. Statistical analysis

The reliability (i.e. internal consistency) of the whole questionnaire was assessed by Cronbach’s α and was considered acceptable for group comparisons if the coefficient exceeded 0.70, as recommended by Nunnally29. Cronbach’s α tests whether the items in a questionnaire have a homogeneous content with respect to the construct of interest. Two indirect methods to evaluate validity of the quality of life instrument were adopted: First, by examining the correlation among the three scales within the instrument, by means of the spearman’s rho coefficient30. Secondly, by assessing the correlation between scale scores and Karnofsky performance status, again using spearman’s rho coefficient. All 37 patients were used in order to assess the validity and reliability of the instrument.

The Kaplan-Meier method and log-rank test were used for the comparative assessment of overall survival between the two groups of patients (group A vs B). The impact to survival of both advanced stage (IV-A and IV-B) and anatomic location of disease (ALD), by means of the primary site in the head versus every other site in the organ, were also analysed using the Kaplan-Meier method and log-rank test31. The statistical difference of 2-years actuarial survival of group B vs A was assessed using the Gehan test30. The patients’ age and possible prognostic factors such as stage of disease, anatomic location of tumour in pancreas and application of IOHT contributing to overall survival were assessed using the Cox-regression model32, in order to determine their contribution to the risk of death. Cox regression analysis was conducted in two steps. In step 1; univariate regression was estimated individually for each possible prognostic factor. In step 2, all prognostic factors from the univariate model were entered into a forward stepwise selection routine (likelihood ratio criterion, χ² model p for entry = 0.05). In group A, thermal parameters concerning $T_{min}$, $T_{max}$ and cumulative minutes $T_{90} ≥ 44°C$ were correlated with overall survival by using the non-parametric Spearman correlation coefficient. Likewise, the Spearman test was used for correlated the post-resection levels of serum CA19-9 with overall survival in all patients. The statistical difference between groups A and B by means of variables based on Karnofsky performance status, Scott-Huskisson visual-analogue pain scale, quality of life scores and serum CEA, as well as CA19-9, were evaluated using the Mann-Whitney non-parametric test30. The statistical significance in the decrease of serum CEA and CA19-9 were assessed by the Wilcoxon test30. All the analysis was performed using the Statistical Packet for Social Sciences for windows (SPSS® v6.0, SPSS, Inc., Chicago, USA).

3. Results

3.1. Toxicity

Toxicity related to multi-schedule chemotherapy was as follows: myelosuppression occurred in 32 patients (86.5%), increase of BUN and/or creatinine were observed in five patients (13.5%), increase of SGOT and/or SGPT were seen in 15
therapy was observed in 30 patients (81%). Gastrointestinal symptoms and alopecia were observed in almost all patients, but all of these toxicities were mild and transient and did not impede the continuous treatment. The median length of post-operative hospital stay after IOHT treatment was 12 days (range 10–15 days). The median length of post-operative hospital stay after by-pass only surgery was 10 days (range 9–12 days). Hiccup and belches were observed exclusively in all group-B patients, lasting for nearly 10 days post-by-pass surgery, which obviously has to be related to IOHT with an unknown mechanism. Two patients from group A and one patient from group B presented grade I mild gastritis according to the RTOG toxicity scale as an acute effect related to radiotherapy. Glucose and amylase determinations remained within normal limits throughout the whole multi-modality treatment. Post-operatively (3–5 days after surgery), glucose was at the upper normal range (101±8 mg/dl) as well as amylase (79±3 U/L).

3.2. Measurements with the QoLBI

Cronbach α coefficients for activity, health status and psychological state scales were 0.75, 0.77 and 0.76, respectively, indicating a good status of internal consistency for the instrument. Spearman-rho coefficient \( r_s \) for correlation between the tree scales of the instrument was as follows: activity to health status \( r_s = 0.65 \), activity to psychological state \( r_s = 0.41 \) and health status to psychological state \( r_s = 0.83 \) \((p < 0.05, \text{in all cases})\). Overall quality of life scale was also significantly \((p < 0.05)\) correlated with activity, health status and psychological state scales \((r_s = 0.81, 0.78 \text{ and } 0.64, \text{respectively})\). Karnofsky performance status was significantly \((p < 0.05)\) correlated with activity, health status and psychological state scales in terms of spearman-rho coefficient \((r_s = 0.71, 0.73 \text{ and } 0.44, \text{respectively})\), indicating that the instrument was sensitive in performance status changes. Consequently, validity and reliability were satisfactory for the QoLBI. Mean score of quality of life according to QoLBI at baseline measurements for groups A and B were 42.9 (±7.9) and 42.1 (±8.2), respectively. One month after the multi-modality treatment, the mean score of quality of life (QoLMS) for groups A and B were 62.5 (±4.9) and 73.7 (±6.3), respectively. Improvement in quality of life was recorded as 42.8% in group B vs 31.3% in group A \((p = 0.031, \text{Mann-Whitney test})\). The above measurements according to QoLBI are shown in figure 2.

3.3. Clinical response

By CT-scan follow-up, the local resectability of the tumour changed in two of the 10 cases undergoing IOHT (group B) after 3 and 9 months, respectively. Among these two cases, one patient already had hepatic metastases excluding any operation. The other patient was planned to undergo a second operation. Unfortunately, in evaluating new CTs before the operation (1 month after), hepatic metastases were revealed. After that, any further consideration for surgery was stopped. No change in resectability was noticed in group A. For group A, there was a significant decrease in both values of serum CEA \((p < 0.001, \text{Wilcoxon test})\) and CA19-9 \((p < 0.001, \text{Wilcoxon test})\), from 7.3 ±1.1 and 798.6 ±130.2 down to 3.5 ±0.7 and 66.6 ±11.5, respectively. Likewise, for group B, there was also a significant decrease in both values of serum CEA \((p = 0.002, \text{Wilcoxon test})\) and CA19-9 \((p = 0.002, \text{Wilcoxon test})\), from 7.6 ±1.3 and 875.7 ±104.8 down to 3.5 ±0.7 and 65.3 ±14.1, respectively. However, there was no significant difference in the decrease.
Additionally, there was also no significant difference in the decrease of CA19-9 ($p \approx 0.15$, Mann-Whitney test) in group A (731.9 ± 128.1) vs group B (810.4 ± 98.4). The mean post-operation CA19-9 level for all patients was 66.16 ± 12.26 U/ml. Post-resection values of CA19-9 did not correlate with overall survival ($\text{Spearman} \rho = 0.03, p = 0.86$). Characteristics of hyperthermia treatment regarding results of $T_{\text{min}}$, $T_{\text{max}}$, and cumulative minutes $T_{90} \geq 44^\circ\text{C}$ for group B patients are shown in table 3. There was a significant correlation of overall survival with $T_{\text{min}}$ ($p = 0.043$), $T_{\text{max}}$ ($p = 0.027$) and CUM MIN $T_{90} \geq 44^\circ\text{C}$ ($p < 0.001$) as well, by means of Spearman test ($\rho = 0.62$, 0.64 and 0.79, respectively).

A significant reduction of the initial persistent pain was observed, after surgery and IOHT, in all patients of group B since a mild analgesic (700 mg aspirin/24 h) was sufficient to achieve pain relief. According to the Scott-Huskisson pain scale, after the combined treatment there was a significant reduction of pain with a mean value of BSHPS of 3.10 ($\pm 0.32$) in group B vs 0.22 ($\pm 0.97$) in group A ($p < 0.001$, Mann-Whitney test). Moreover, there was also a significant improvement after the combined treatment in Karnofsky performance status, with a mean value of BKPS of 28.0 ($\pm 0.6$) in group B vs 9.3 ($\pm 11.1$) in group A ($p < 0.001$, Mann-Whitney test).

According to computerized tomography evaluations, the radiological response to disease is shown in table 4. Local control related to combined treatment modality seems better in group B ($p < 0.001$, $\chi^2$ test), since no progressive disease was noticed after IOHT. All the patients in group B died due to liver metastases, with emphasis to the fact that no obstruction was recorder during follow-up. The cause of death for group A patients was liver metastases and mainly local progressive disease (obstruction). The patients of group B had a 2 year actuarial survival of 10% (95% CI: 5.2–14.8) after the treatment vs 3.7% (95% CI: 2.1–5.3) for patients in group A ($p = 0.0075$, Gehan test).

In one patient from group B (case 1) with the shortest survival, it was not possible to provide therapeutic temperatures throughout the entire tumour by using either one of the available applicators, due to the large extent of tumour compared to the effective field size of both applicators. Survival curves for patients in groups A and B are shown in figure 3. The median overall survival for patients in group B was 11.00 months (SE = 2.37) in contrast to 7.00 months (SE = 0.46) for patients in group A.
The application of IOHT ($p = 0.034$), the stage IVA ($p = 0.024$) and the adenocarcinoma located at the head of the pancreas ($p = 0.025$) have a positive impact to survival, and age seems to have no impact ($p = 0.42$). These factors were subsequently tested on a multivariate model in terms of stepwise Cox-regression analysis. Thus, the only significant effect on overall survival was due to stage ($p = 0.004$) and application of IOHT ($p = 0.011$) as independent factors, while the ALD lost its prognostic value ($p > 0.05$). The Cox-proportional hazard model revealed that the relative risk of death for metastatic stage (IVB) and patients not undergoing IOHT were 3.07 and 2.94, respectively. Moreover, according to the log-rank test, patients with tumour seated in the head had a median survival of 11 months (SE = 0.99) vs 6 months (SE = 0.27) for tumours located in the body or tail ($p = 0.007$). Patients with metastatic disease to liver (stage IVB) had a median survival of 6 months (SE = 0.28) vs 11 months for patients without liver metastases as stage of disease and ALD were assessed in terms of univariate cox-regression analysis (table 5). The application of IOHT ($p = 0.034$), the stage IVA ($p = 0.024$) and the adenocarcinoma located at the head of the pancreas ($p = 0.025$) have a positive impact to survival, and age seems to have no impact ($p = 0.42$). These factors were subsequently tested on a multivariate model in terms of stepwise Cox-regression analysis. Thus, the only significant effect on overall survival was due to stage ($p = 0.004$) and application of IOHT ($p = 0.011$) as independent factors, while the ALD lost its prognostic value ($p > 0.05$). The Cox-proportional hazard model revealed that the relative risk of death for metastatic stage (IVB) and patients not undergoing IOHT were 3.07 and 2.94, respectively. Moreover, according to the log-rank test, patients with tumour seated in the head had a median survival of 11 months (SE = 0.99) vs 6 months (SE = 0.27) for tumours located in the body or tail ($p = 0.007$). Patients with metastatic disease to liver (stage IVB) had a median survival of 6 months (SE = 0.28) vs 11 months for patients without liver metastases.
4. Discussion

Pancreatic adenocarcinoma continues to be appraised as a neoplasm with dismal prognosis. The importance of improving therapy for this disease is accentuated by its increasing incidence in recent years and also by the fact that local tumour can cause prolonged and severe problems related to anorexia, pain, bleeding and obstruction. The vast majority of patients are diagnosed with locally advanced unresectable disease. For advanced stage of pancreatic cancer, the main modalities that have been used with confirmed clinical benefits are based on palliative surgery\(^1\)\(^-\)\(^5\), 5-Fluorouracil chemotherapy alone or combined with radiation\(^7\)\(^-\)\(^10\) and external beam of radiotherapy\(^7\); definitely, there is a role for additional therapy regarding patients with advance pancreatic cancers\(^3\)\(^4\). Pre-operative chemo-radiotherapy has also shown promising results\(^3\)\(^5\)\(^-\)\(^36\). However, although neoadjuvant chemoradiation has many theoretical advantages in managing pancreatic malignancy, true pathologic downstaging of locally advanced lesions into tumours that can be removed with negative nodes and margins appears to be a rare event with currently used therapeutic regimens\(^3\)\(^7\).

Beyond the questionable role of pre-operative chemo-radiotherapy, it was decided to investigate the combination of intra-arterial 5-FU in conjunction with intra-operative hyperthermia. As an argument for this schedule arises from the previous literature, reporting interaction of heating with 5-FU. Matsuoka et al.\(^2\)\(^1\) demonstrated the enhancement role of hyperthermia in the cytotoxic effect of 5-FU. Lubbe et al.\(^3\)\(^8\) studied the microcircularity effects of hyperthermia and 5-FU in mice-skin and concluded that external heating generates skin-perfusion limiting the amount of cytostatic fluoracil in the heating-region. Shchepotin et al.\(^3\)\(^9\) showed that 5-FU, verapamil and hyperthermia significantly decreased in-vitro lines of human pancreatic adenocarcinoma by 63.8% compared to the control. Maeta et al.\(^4\)\(^0\) analysing the effects of hyperthermia on metabolism of 5-FU in vitro, reported that high temperature (\(>42^\circ C\)) results in the increased delivery of 5-FU and low temperatures at 39°C induces an enhanced antitumour effect of 5-FU via an increased rate of metabolism of 5-FU. Far from this, somatostatin (SST) and its analogues are candidates for use as endocrine agents in the treatment of pancreatic

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>Relative risk</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>CI*</td>
</tr>
<tr>
<td>Stage (IVB vs IVA)</td>
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</tr>
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<td>ALD (body and/or tail vs head)</td>
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</tr>
<tr>
<td>Group A vs group B</td>
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<td>2.55</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.18</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>0.42</td>
<td>—</td>
</tr>
</tbody>
</table>

* 95% confidence interval (lower-upper limit).
without tamoxifen was effective as a growth-inhibitory factor against SKI human pancreatic cancers during in-vivo studies in nude mice. Recently, Tang et al.\textsuperscript{42} demonstrated that both pancreatic adenocarcinoma and gastrinoma expressed specific SST receptors. By summarizing, both of the previous mentioned regimens (5-FU and somatostatin) were used in the clinical study, due to the potential therapeutic effect against pancreatic adenocarcinoma with emphasis to the synergistic effect of hyperthermia and 5-FU. However, a recent report by Burch et al.\textsuperscript{43} concerning a randomized study, showed no clinical benefit for octreotide in metastatic pancreatic cancer. Moreover, multiagent chemotherapy for inoperable cases including the combination of 5-FU, doxorubicin and cisplatin (FAP) have minor activity in the adenocarcinoma of the pancreas, although there is reported a response rate up to 15\%\textsuperscript{10,44}. Nevertheless, many chemotherapeutic agents have been evaluated in patients with pancreatic cancer with an indication of improvement in survival and quality of life, but the magnitude of this effect is negligible\textsuperscript{45,46}.

Previously, the Gastrointestinal Tumour Study Group reported a significant benefit in overall survival by using combination of radiotherapy and 5-FU for the treatment of locally advanced pancreatic tumour\textsuperscript{47}. However, radiotherapy as an adjuvant treatment modality has already been used in many recent clinical trials but with modest clinical benefit\textsuperscript{7,48}. Moreover, in a recent report, Neoptolemos et al.\textsuperscript{49} regarding interim results of a major randomized study, showed surprisingly no benefit to adjuvant radiotherapy in resectable pancreatic cancer. The need for new treatment modalities for the management of unresectable pancreatic adenocarcinoma arises more and more demanding. The potential role of hyperthermia in conjunction with radiotherapy in the treatment of cancer is already known\textsuperscript{50,51}. Under these circumstances, a place for the intraoperative hyperthermia constituting a multimodality treatment seems quite reasonable\textsuperscript{19,34}. Merrick et al.\textsuperscript{52} presented a patient with unresectable metastatic adenocarcinoma in the left paravertebral area. The disease had not responded to external beam radiation therapy. The tumour was approached through a thoraco-abdominal incision and intra-operative hyperthermia was delivered via interstitial electrodes. The patient recovered without complication and had complete relief from pain, and post-treatment CT scans have demonstrated control of disease for over a 5-month follow-up period. Colacchio et al.\textsuperscript{16} studied morbidity and mortality from combined intra-operative radiotherapy and intra-operative hyperthermia treatment for unresectable intra-abdominal carcinomas. The morbidity (58\%) and mortality (11\%) rates reported in that series were comparable to rates reported in series of similar patients receiving intra-operative radiation therapy alone. Ashayeri et al.\textsuperscript{18} reported a post-operative survivorship averaged up to 15.8 months for five patients with unresectable pancreatic adenocarcinoma that were treated with simultaneous intra-operative radiotherapy and intra-operative hyperthermia. Ryan et al.\textsuperscript{17} studied 19 patients that were heated with ultrasound in the operating room during surgical resection. Immediately following intra-operative radiation therapy, thermocouples were inserted into the tumour and adjacent normal structures. Patients were then given a 60-min ultrasound heating with an average of the maximum temperatures attained of 46.6\degree C.

All previous reports concerning intra-operative hyperthermia can be summarized into two major conclusions: significant pain relief and a slight benefit in survival. The 10 cases included in the present report concerning the application of intra-operative hyperthermia in conjunction with post-operative radiotherapy and multi-schedule
very serious problem of advanced pancreatic cancer, and warrants further consideration with many more patients. In contrast to external deep-heat, local intra-operative hyperthermia seems to be more effective in achieving therapeutic temperatures in the tumour. The exceptional efficacy of measuring temperature inside the tumour intra-operatively has been mentioned by other authors and needs to be emphasized. According to these results, only one patient (10%) failed to be heated properly in the hyperthermia range of 42.5–45°C. This is in contrast to the Yamada et al. study, where the failure for sufficient heating was up to 71%. This difference might be due to the low emitted power and the type of capacitive device that was used. On the other hand, there was a significant correlation between survival and thermal parameters such as $T_{\text{min}}$, $T_{\text{max}}$ and CUM MIN $T_{90} \geq 44^\circ\text{C}$. This observation is in agreement with other authors raising the role of the latter variables as prognostic factors for local control of the disease. Another argument for raising the role of sufficient heating as prognostic factor comes again from Yamada et al. observations where obtained temperatures of higher than 42°C were leading benefits in median survival (from 5.5–9 months). The results concerning the sufficient heating of the tumour were more or less expected, due to experimental measurements that have been performed in reliable phantoms showing a penetration depth (50% of maximum SAR) of up to 3 cm. The initial focus of this study was the efficacy of a multi-modality approach, including intra-operative hyperthermia, to the treatment of pancreatic tumours and to make assessments about the benefit in survival and quality of life. Patients with a performance status of 50–60 were also allowed to enter the protocol. These patients had a typical pancreatic cancer related back-pain. They were allowed to have the multi-modality treatment for two reasons: first, it was a salvage treatment and, moreover, the results showed a significant improvement in the performance status that was recorded after the treatment; secondly, this multi-modality study doesn’t represent an aggressive type of treatment, since the morbidity that was finally recorded was rather moderate.

Although randomization was initially intended, this study was unable to be completed in a randomized fashion due to complexities of randomizing patients after enrollment for a surgical procedure shortly before the procedure was planned. While this may lead to selection biases and may result in important differences between patients recruited in groups A and B, eventually patients were enrolled into this study as candidates for either arm, and all data were gathered prospectively. Thus, this study should be regarded as a combination Phase I/II prospective trial to evaluate tolerability and possible clinical benefit. The problem with the patients’ refusal to undergo intra-operative hyperthermia was only related to the study’s informed consent, where it was written that the additional intra-operative treatment would last for more than 1 h after the major(initial surgery. Many patients felt that the risk-to-benefit ratio was not favourable.

In the present approach, by introducing the intra-operative application of hyperthermia, it was possible to heat pancreatic tumours effectively without causing any damage to neighbouring normal tissues, in contrast with devices aimed at heating deep seated tumours, which produced severe subcutaneous fatty burns. The median survival of patients who underwent additionally IOHT (group B) was 11 months vs 7 months concerning patients who did not receive IOHT. Several studies with radiotherapy (without IOHT) in unresectable pancreatic adenocarcinoma reported a median survival neither more or less excited 9 months after diagnosis. Even
Intraoperative hyperthermia and multi-schedule chemotherapy

upper limit for unresectable pancreatic carcinoma\textsuperscript{56}, in contrast to intra-operative RT where the median overall survival seems to be slightly better\textsuperscript{57}. The 10\% of 2 year actuarial overall survival in group B agrees with survival rates reported by Yamada \textit{et al.}\textsuperscript{19} for patients with pancreatic cancer undergoing hyperthermia. The results have shown that intra-operative hyperthermia combined with 5-FU may have an anti-tumour effectiveness due to a better overall survival achieved and, beyond this, it was well tolerated by the patients, since neither peri-operative nor post-operative moderate toxicity related to IOHT was noticed. However, the hiccup and belches that were observed post-by-pass surgery exclusively in all group B patients were mild and may be related to a small inflammation of the pneumogastric plexus during IOHT. Although definitive conclusions are primitive, the results in terms of log-rank test ($p = 0.0029$) and cox-regression multivariate analysis ($p = 0.011$) suggests that for pancreatic cancer the administration of intra-operative hyperthermia may prolong survival. Additionally, disease without liver metastases and tumours seated in pancreatic head seem to have a better response by means of a significant difference in median survival (log-rank test) and positive impact on survival in univariate cox-regression survival model, a fact that has been mentioned before\textsuperscript{58,59}. The fact that metastatic disease kept its prognostic value in the multivariate model was more or less expected\textsuperscript{46}. Although in the multivariate model the prognostic value of IOHT was lower than the prognostic significance of metastatic stage, anatomic location of disease lost its prognostic value in the final cox-proportional model. Moreover, sex had no prognostic value, even in the univariate model. These important remarks may be an indirect method of minimizing the inhomogeneity of sex and tumour-location recorded between groups A and B. However, the problem of insufficient number of patients continues to exist. Concerning the decrease of serum CEA and CA19-9, no significant difference was assessed between groups A and B. This fact is highly related with the absence of any correlation between survival and post-resection CA19-9 levels. These results are in agreement with Abrams \textit{et al.}\textsuperscript{60} observations. With regard to symptomatic control, all of the patients with significant pre-treatment symptoms claimed substantial or complete relief during the follow-up period. Performance status, pain score and quality of life score were statistically more improved in group-B vs group-A patients. Although the present study is only a small series of patients, this significant improvement should not be underestimated.

In preparing the clinical protocol, special emphasis has been given to the assessment of quality of life, since any considerable quality of life benefits from hyperthermia application should be measured according to the most important aspects of health, as well as focusing on important particular problems in cancer patients\textsuperscript{61}. The four scales (Activity, Health Status, Psychological state, and Overall Quality of Life) of the quality of life instrument were not \textit{a priori} correlated with each other. The instrument was developed for cancer patients suffering from gastrointestinal malignancies, and the validation especially for pancreatic cancer stands in need in order to confirm reliable results. This small study was not intended to validate a QoL instrument but to expand its validation for pancreatic cancer. Concerning multi-parameter assessments regarding performance status, almost similar but not identical parameters used for evaluation were the Scott-Huskisson pain scale, the Karnofsky scale and the quality of life score. That was for two reasons: first all these parameters were selected \textit{a priori} and evaluated during the trial as endpoints from the very
representing the patients’ status were welcome for the validation of measurements that are \textit{a-priori} qualitative and not quantitative. Furthermore, with regard to the choice of the chemotherapeutic agent and the way of combining modalities reported here, it is not ideal, since the toxicity remains moderate and the current literature mainly contains reports of minimal efficacy\textsuperscript{10,46}. Thus, the combination of 5-FU plus doxorubicin plus cis-platin is an old regimen with limited effectiveness for pancreatic cancer. Although there is no standard chemotherapy treatment for pancreatic cancer, most oncologists consider gemcitabine as a standard of care. Indeed, in a recent randomized study for advanced pancreatic cancer, single-agent gemcitabine was shown to be superior to single-agent 5-FU\textsuperscript{62,63}. Moreover, in a recent report by Burch \textit{et al}\textsuperscript{43}, octreotide does not delay progression or extend survival in patients with advanced pancreatic cancer compared with standard treatment with 5-fluorouracil. The dosage and schedule of chemotherapy administration and the exact thermal dose that would enhance direct cytotoxic effects in the pancreatic adenocarcinoma must be investigated in a randomized study to determine the efficacy of each one. Improved programmes of IOHT with sufficient and accurate control of the applied thermal dose, together with the development of more effective combinations of chemotherapeutic agents, may further enhance the effectiveness of the combined treatment. Nevertheless, further investigations are necessary, in order to estimate the most effective schedule of the multi-modality treatment reported in this manuscript (pre- vs post-operative chemo-radiation).

In closing, according to the results of the multivariate cox-regression analysis described in table 5, there is nearly 2.94 (95\% CI: 1.29–6.69) times the relative risk of death for the patients who did not undergo IOHT. Although it seems that there is a trend of clinical benefit regarding intra-operative hyperthermia, no definite conclusions can be made. Several reasons are responsible for this: (1) this is not a randomized study; (2) the number of patients is quite small; (3) there is a possible bias in the selection of the patient; and (4) possible prognostic factors such as the location of disease (head vs body/tail) and sex (male vs female) are distributed in an inhomogeneous way between groups A and B. The results presented here should serve as stimulus and foundation for the continued study of multi-modality therapy in the management of unresectable adenocarcinoma of the pancreas. Definitely, combined modality treatments are superior to irradiation alone\textsuperscript{64}. However, the resectability of the tumours, even after IOHT, was not changed significantly. One may comment on this by emphasizing two facts: first, many patients had already presented hepatic metastases, making the decision of a second operation definitely negative; and secondly, the total irradiation dose of 45 Gy might be low, since in many reported trials the total dose was 50 Gy or more\textsuperscript{7}. However, beyond this, moderate or high dose irradiation is unlikely to convert a truly unresectable tumour to a resectable lesion\textsuperscript{7}.

The aim of this study was to share the authors’ experience for the common effort of many experts in oncology, surgery, radiotherapy and biomedical engineering in giving a promising additional therapy advanced pancreatic adenocarcinoma. Further clinical trials for investigating the clinical benefit of IOHT are strongly recommended.

References
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22. Emi Y, Kohnoe S, Yoshida M, Takahashi I, Maehara Y, Sugimachi K. Hyperthermia enhances the inhibition of tumor growth by 1-(2-tetrahydrofuryl)-5-fluorouraciluracil (1:4)


Appendix: Quality of Life Brief Instrument (QoLBI)

During the past week:

<table>
<thead>
<tr>
<th>Activity</th>
<th>No</th>
<th>Sometimes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) I keep working or doing housechores</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(b) I am capable on doing strenuous activities (carrying heavy objects)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(c) I am able to take a short walk</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(d) Self sufficient (dressing or physical hygiene etc.)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health status</th>
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<th>Sometimes</th>
<th>Yes</th>
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<tbody>
<tr>
<td>(a) I feel pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(b) I feel lack of appetite</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(c) I feel weak and/or tired</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>Psychological state</th>
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<td>(a) I feel calm</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(b) I feel optimistic</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(c) I continue every social or family activity that pleases me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Overall Quality of Life
Please estimate your Quality of Life using the following scale

0 1 2 3 4 5 6 7 8 9 10
Poor Excellent