Pseudomyxoma peritonei treated with complete resection and immediate intraperitoneal chemotherapy

Dominique ELIAS (1), Stanislas LAURENT (1), Samy ANTOUN (2), Pierre DUVILLARD (3), Michel DUCREUX (4), Marc POCARD (1), Philippe LASSER (1)


SUMMARY

Aim — Pseudomyxoma peritonei remains a fatal disease. This clinical pathological entity based on the presence of mucin includes different prognostic groups. Complete resection of macroscopic lesions, combined with immediate intraperitoneal chemotherapy to treat remnant infra-millimetric disease, might improve survival. The aim of this prospective study was to evaluate this treatment strategy.

Methods — Thirty-six patients with pseudomyxoma peritonei underwent resection of supra-millimetric lesions then were given either postoperative intraperitoneal chemotherapy (5 days) before January 1996) or intraoperative chemohyperthermia treatment (after January 1996). During this same period, only partial resection of the macroscopic lesion was possible in 15 patients; these patients were not given peritoneal chemotherapy.

Results — Postoperative mortality was 13.8% (n = 5), including 2 deaths not specifically due to the procedure. Morbidity, including severe and non-severe complications was 44%. After a mean follow-up of 48 months, the overall 5-years survival rate was 66%, and disease-free survival rate was 55% (including the postoperative deaths). The main prognostic factor in this series was the pathological grading; 5-years survival was 74% for grade 1 tumors versus 54% for grades 2-3 (P = 0.05).

Conclusion — The main prognostic factor of the pseudomyxoma peritonei, after the completeness of the resection, is the pathological grading. The addition of an intraperitoneal chemohyperthermia improves long-term survival of grades 2-3 tumors and perhaps that of grade 1 (agreement of experts). This treatment is more easily performed, more well-tolerated, and more efficient when performed early.

RÉSUMÉ

Pseudomyxomes péritonéaux traités par exérèse complète et chimiothérapie intrapéritonéale immédiate

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Objectif — Le pseudomyxome péritonéal est une entité clinico-pathologique basée sur la présence de mucine et qui recouvre des formes évolutives différentes mais toujours fatales. L’exérèse complète des lésions macroscopiques combinée à une chimiothérapie intrapéritonéale immédiate pour traiter la maladie infra-millimétrique résiduelle est une nouvelle thérapeutique susceptible d’en améliorer la survie. L’objectif de cette étude prospective était d’évaluer ce traitement.

Méthodes — Trente-six malades ont été traités par résection chirurgicale des lésions supra-millimétriques et, soit par une chimiothérapie intra-péritonéale postopératoire immédiate pendant une durée de 5 jours (avant janvier 1996), soit par une chimio-hyperthermie intrapéritonéale péritonéale après janvier 1996. Durant la même période, 15 autres malades n’ont pu être traités que par exérèse incomplète sans chimiothérapie intrapéritonéale.

Résultats — La mortalité opératoire a été de 13,8% (n = 5), mais 2 décès n’étaient pas spécifiquement imputables à la procedure. La morbidité a été de 44 %, incluant aussi bien les complications majeures que mineures. Après un recul moyen de 48 mois, la survie globale à 5 ans était de 66 % (mortalité postopératoire incluse), et la survie sans récidive de 55 %. Le principal facteur pronostic dans cette série a été le grade histologique du pseudomyxome : survie à 5 ans de 74 % pour les tumeurs de grade 1 et de 54 % pour les tumeurs de grades 2 et 3 (P = 0,05).

Conclusion — Le principal facteur pronostique des pseudomyxomes péritonéaux, après l’exérèse complète des lésions, est le grade histologique. L’ajout d’une chimio-hyperthermie intrapéritonéale améliore la survie des tumeurs de grades 2-3 et peut-être celle des tumeurs de grade 1 (accord d’experts). Ce traitement est d’autant plus simple, mieux supporté et d’autant plus efficace que le malade est traité précocement.

Pseudomyxoma peritonei (PMP) is a rare clinical and poorly understood pathological entity characterized histologically by the presence of a predominant mucin component. Clinical expression ranges from benign disease to fatal malignancy. Appropriate treatment is difficult to establish due to the small number of patients, possible confusion between appendicular or ovarian disease, the different grades of malignancy, and the different treatment protocols proposed to date (abstention, extensive resection, heated intraperitoneal chemotherapy, symptomatic surgery as requested).

Dissatisfied with the poor results obtained after repeated surgery for incomplete resection, we conducted a prospective study for complete resection and intraperitoneal chemotherapy.
study enrolling thirty-six patients treated between 1994 and 2000 combining complete cytoreductive surgery with immediate postoperative intraperitoneal chemotherapy (IPIC) for 5 days and later with additional heated intraoperative intraperitoneal chemotherapy (HIIC). This protocol was based on the curative approach to peritoneal carcinomatosis proposed in 1988 by Sugarbaker et al. [1]: cytoreductive surgery to remove macroscopic disease (since intraperitoneal chemotherapy does not penetrate more than 1-2 mm) followed by high-dose local regional chemotherapy delivered perioperatively before the tumor cells can become trapped in adhesions to treat the microscopic residual tissue causing recurrence. This curative approach has been applied in patients with peritoneal carcinoma due to adenocarcinoma of the colon and has demonstrated a certain degree of success [2, 3].

The purpose of the present work was to report our findings in a prospective series of 36 patients with pseudomyxoma peritonei who underwent complete cytoreductive surgery and perioperative chemotherapy (IPIC or HIIC).

Patients

Between January 1994 and January 2001, we attempted to achieve cure in 51 patients with PMP using a treatment protocol combining macroscopically complete cytoreductive surgery and perioperative chemotherapy [IPIC (1994-1995) or HIIC (1996-2000)]. During this period, cytoreductive surgery was considered complete in 36 patients and incomplete in 12 (as expected preoperatively in 6 of them). At laparotomy, tumor reduction was found to be impossible in 3 patients. The prospective series thus included 36 patients (36/51, 70%) who had optimal chances of cure after complete macroscopic resection. There were 22 women and 14 men, mean age 47.8 ± 9.4 years (median 47, range: 27-66). All patients had undergone at least one previous laparotomy for PMP (one for 16, two for 13, three for 7). The preoperative work-up included a physical examination, a computed tomography of the abdomen and the thorax, and CEA, Ca 19.9, and Ca 125 assays. These patients who gave their informed consent had been referred to our unit for this specific protocol designed to maximize the chances of cure. The study was performed within the framework of three successive therapeutic trials conducted in compliance with French legislation (Huriet law).

Methods

The extent of PMP dissemination was described in detail at the beginning of the surgical procedure using the scoring system proposed by Sugarbaker [4] (figure 1). This system assigns a score of 0 to 3 for 13 regions of the abdomen giving a total score ranging from 1 to 39.

Surgery was performed to remove or destroy all macroscopically detected disease, such that no nodules greater than 1 to 2 mm were left in place. When residual diseases greater than this defined size was present, no intraperitoneal chemotherapy was delivered. Generally, the peritoneum was completely resected. Tumor nodules or gelatinous deposits measuring 1-5 mm were destroyed by electrodestruction in some cases if they were located on the walls of the small bowel, the stomach, the liver, or the diaphragm. Electrodestruction was achieved by galvanocautery using the “section” setting at maximum power to volatize the seeded tumor deposits. Vapors were extracted with an aspiration device (Airsafe ES2000, Stakhouse, USA) and the tissue surface was immediately cooled with cold saline solution. All infiltrated tissue was resected.

The immediate intraperitoneal chemotherapy was delivered with the IPIC protocol at the beginning of our experience then with the HIIC protocol. Modalities of these local treatments varied over the 7 years experience and are described in table I. Retrospectively, we considered that the patients who had had the IPIC protocol (without heated chemotherapy), or were included in the first HIIC trial [5] designed to select the best technical procedure to deliver HIIC or the first part of the second HIIC trial designed to study the pharmacokinetics of heated oxaliplatin delivered intraperitoneally, had not undergone the most optimal procedure. IPIC was used for 4 patients, HIIC followed by IPIC for 9 and HIIC for 23 (including 3 in the first HIIC trial and 6 in the first part of the second HIIC trial). Fourteen patients were thus considered to have received optimal treatment defined as follows: HIIC delivered via a closed circuit with the abdomen held open by upward traction on the skin, heating to 42-44 °C, intraperitoneal infusion of oxaliplatin (460 mg/m² in 2 L/m² 5% dextrose for 30 min) after intravenous infusion of 5-fluorouracil (400 mg/m²) and folate (20 mg/m²) [6].

The histology grades described by Ronnett et al. [7] (table II) were used.

Statistical analysis

Data were recorded prospectively in a dedicated database. Quantitative data were expressed as means ± standard deviation and range. No
patients were lost to follow-up. The chi-square test was used to compare groups with the significance threshold set at 5%. Kaplan-Meier survival curves were plotted and compared with a unifactorial log-rank test.

**Results**

**Intraoperative findings**

Pseudomyxoma peritonei involved 11.1 ± 3.6 of the 13 regions of the abdomen (figure 1). The mean dissemination score was 19.6 ± 8.2 (median 21), range: 5-34. Mean operative time was 563 ± 178 min (median 600, range: 285-900). Mean blood loss was 1 856 ± 1 704 mL (median 1 200, range: 200-8 900). Cytoreduction removed all macroscopically detectable malignant tissue (tumor residue = 0 mm) in 23 patients (64%). Residual nodules measuring 1 mm remained in 10 patients (28%) and measuring 2 mm in 3 patients (8%).

On the average, 4.8 ± 2.1 organs were resected (greater omentum, lesser omentum, and peritoneal surfaces excluded) requiring 2.8 ± 2.4 circular digestive anastomoses (median 2, range: 0-7) and 1.4 ± 1.1 lateral closures (median 1, range: 0-3). Suture of the bladder was required in 6 patients, total colectomy in 8 (22%), and remaining short small bowel (< 2m) in 3. The pleura had to be opened in 8 patients during diaphragmatic peritonectomy but no detectable passage into the thorax occurred.

**Postoperative data**

Five patients died before discharge (mortality 13.8%). One patient died from cerebral anoxia subsequent to obstruction of the tracheal tube the first night after surgery. The cause of death at day 12 was rupture of a cerebral aneurysm in another patient. Two patients died from cerebral hemorrhage on day 20 and 22 secondary to thrombopenia in one and microangiopathic in the other. The fifth patient died on day 23 from peritoneal mycosis without associated digestive fistula after development of severe neutropenia (neutrophil count < 500).

Morbidity was 44%, including both severe and non-severe complications. Digestive fistulae developed in 8 patients and deep abscesses in 7 (abdominal complication rate 39%), requiring a revision procedure in 6 patients. Forty-four patients

<table>
<thead>
<tr>
<th>Type</th>
<th>Intraperitoneal chemotherapy</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>IPIC: J1: mitomycin C (10 mg/m²), d2 to d5: 5-FU (1 gr/m²/d)</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>HIIP 1 with mitomycin C 10 mg/m² then IPIC from d2 to d5 with 5-FU 1 gr/m²/d</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>HIIP 1 with mitomycin (20 mg/m²) and cisplatinum (200 mg/m²)</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>HIIP 2 with oxaliplatinum from 260 to 410 mg/m², with IV infusion of folinic acid (20 mg /m²) and 5-FU (400 mg/m²)</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>HIIP 2 with oxaliplatin at 460 mg/m² with IV infusion of folinic acid (20 mg /m²) and 5-FU (400 mg/m²)</td>
<td>14</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

* IPIC = Immediate postoperative intraperitoneal chemotherapy delivered in a continuous infusion for 5 days after surgery; * HIIP 1 = Heated intraoperative intraperitoneal chemotherapy for 60 min at 42 °C using several technical modalities tested successively during the HIIP 1 trial (12); * HIIP2: Heated intraoperative intraperitoneal chemotherapy for 30 min with the abdomen held open by upward traction at 42-43 °C delivered within the framework of the HIIP2 trial conducted to establish the pharmacokinetics of intraperitoneal oxaliplatinum given at stepwise increasing doses (13); 5-FU: 5-fluorouracil

Table I. – The different types of intraperitoneal chemotherapy used successively.

Table II. – Pseudomyxoma peritonei: differential histologic patterns between disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis. (PMCA). From Ronnet et al. [7].

<table>
<thead>
<tr>
<th>Origin</th>
<th>DPAM (grade 1)</th>
<th>PMCA (grades 2-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial tumor</td>
<td>Mucinous adenoma</td>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Gross aspect</td>
<td>Mucinous ascitis, deposits sparing the small bowel</td>
<td>Carcinomatosis, with zones of infiltration</td>
</tr>
<tr>
<td>Peritoneal tumor</td>
<td>Poor</td>
<td>Moderate to abundant</td>
</tr>
<tr>
<td>Cellularity</td>
<td>Moderate to abundant extracellular mucin containing simple or very focal proliferating mucinous epithelium</td>
<td>Moderate to abundant extracellular mucin containing very proliferative mucinous epithelium or isolated or clustered cancer cells</td>
</tr>
<tr>
<td>Morphology</td>
<td>Minimal</td>
<td>Moderate to marked</td>
</tr>
<tr>
<td>Cell atypia</td>
<td>Rare</td>
<td>Few to many</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Invaded lymph nodes</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Invaded neighboring organs</td>
<td>Rare (ovary excepted)</td>
<td>Frequent</td>
</tr>
<tr>
<td>5 year survival</td>
<td>80%</td>
<td>10%</td>
</tr>
</tbody>
</table>
developed an extra-digestive complication, mainly lung infection (n = 12), temporary renal failure (n = 8), and aplasia (grade 3) (n = 7). Intra- and extra-abdominal complications were more frequent when more than 4 organs were invaded (P = 0.04) and when more than two circular anastomoses were fashioned (P = 0.03), but without a significant correlation with operative time or extent of blood loss.

Oral feeding could be resumed after 10 days (median). Median hospital stay was 24 days (mean 32.5 ± 22.1; range: 14-102) for surviving patients.

**Histology**

There were 22 grade 1 tumors (diffuse peritoneal adenomucinosis), 3 grade 3 (peritoneal mucinous carcinomatosis), and 11 grade 2 (peritoneal mucinous carcinomatosis with intermediate or discordant features). Mesenteric lymph nodes were invaded in 6 patients (17%) with grade 2 or 3 tumors. The parenchyma of resected organs (ovary, liver, spleen, tail of the pancreas) was free of tumor tissue in all patients.

**Survival**

Median survival was 48 months (range: 9-104). The overall and disease-free rates of survival at 5 years were 66% and 55%, respectively. The survival curve exhibited a sharp decline at 3 years followed by a plateau (figure 2). Nine of the 32 patients (29%) surviving surgery developed recurrent disease. Among these, 2 of the 5 patients with intraperitoneal recurrence underwent a second procedure for complete cytoreduction and HIIC (to date, both remained disease-free during the short follow-up). The recurrent tumor exhibited a higher histology grade in 4 patients. The recurrent tumor was extra-abdominal in 4 patients: both pleurae in one patient (without injury to the pleura at the first operation), the vaginal resection margin in another, the obturator foramen in the third, and the lateral aortic lymph nodes in the fourth. None of these 4 patients achieved complete remission after recurrence.

At last follow-up, 10 of the 36 patients (28%) had died: 5 during the postoperative period, 4 due to recurrent PMP, and 1 suicide. Among the 26 survivors, 23 (83%) were disease-free. Five-year survival was better for patients with grade 1 tumors than those with grade 2 or 3 tumors (74% and 54%, respectively, P = 0.05). Conversely, degree of PMP dissemination, as reflected by the peritoneal score (using a cutoff at 20), did not appear to influence prognosis.

**Discussion**

Pseudomyxoma peritonei results from the presence in the peritoneum of mucus-secreting neoplastic cells, which, when searched for with an appropriate technique [7], can always be detected. Patients with PMP develop a characteristic gelatinous (or more appropriately mucinous) ascites associated with mucinous and cellular implants on the peritoneum. In our experience, fluid “gelatinous” ascitis is less common than more compact tumor formations. The clinical term of “gelatinous disease” should thus be abandoned because it is rather limiting (only the first type of presentation is included) and imprecise (risk of confusion with low-grade malignant ovarian mucinous tumors). Thus, the term PMP includes a group of neoplastic conditions characterized by a more or less compact accumulation of mucus in the abdomen. Specific clinical and radiological presentations can be described but the histological substrata and potential treatments and prognosis are quite different.

In a large majority of patients (80%), PMP arises from appendicular disease and not ovarian disease [8] although ovarian seeding, observed in nearly 90% of the female patients may be misleading [9]. PMP is often mistaken for a mucinous ovarian tumor. Advances in immunohistochemistry and molecular biology have greatly contributed to the debate concerning the appendicular or ovarian origin of PMP. The molecular profiles generally exhibit a colorectal rather than an ovarian pattern [10]. Furthermore, K-ras gene mutations and allele losses on chromosomes 18q, 17p, 5q, and 6q, observed in PMP, are not found in true borderline tumors of the ovary [11]. This nosological distinction is important because of the difference in prognosis: 5-year survival reaches 95-100% for low-grade mucinous tumors of the ovary, but falls to 75-80% for minimally aggressive PMP and less than 10% for aggressive PMP [12]. In women, very predominant fluid gelatous ascitis is more suggestive of peritoneal dissemination of a low-grade malignant mucinous tumor of the ovary. Molecular biology techniques difficult to implement in routine practice are required for definite diagnosis. These patients should thus undergo classical surgery in an attempt to achieve complete resection, the diagnosis of appendicular PMP then being retained in event of recurrence, although true PMP can also arise from other organs (ovary, pancreas, colon, bronchi) [8]. Finally, PMP is difficult to study because it is a very rare disease; occurring in 2 of 10 000 laparatomies [13].

The classical definition of PMP based on the presence of a large quantity of mucin in the peritoneum is insufficient. Ronnet et al. [7, 10, 12] made an important contribution by identifying 3 distinct histopathological grades of PMP with very different prognoses. These authors studied the tumor “shell” designated as the zones of mucinous epithelial cell implantation on peritoneal surfaces. They described a grading system based on distinctive features of the shell such as single or multiple layers, cell atypia, and mitosis index (table II). In clinical practice, there is very little difference in the prognosis for grade 3 PMP (mucinous peritoneal carcinomatosis) and grade 2 PMP (an intermediary grade between grades 1 and 3 where adenomucinosis predominates but with associated foci of mucinous adenocarcinoma). It might be useful to group these two grades together.

There is no consensus on standard treatment for PMP and data in the literature do not lead to clear conclusions. We nevertheless considered that systemic chemotherapy is currently ineffective [14, 15] and that surgical resection should remain the fundamental treatment. Unfortunately, most reports have omitted a detailed description of the tumor mass (minimal or massive PMP), its consistency (from liquid to a solid form), the physiological status of the patients, the histological grade, or the completeness of the cytoreduction [14, 16, 17]. In addition, surgery for PMP is generally limited to resection of the more accessible central and gelatious lesions without removing the peripheral visceral and parietal peritoneum which is the site of the active neoplastic process. Consequently, mucin-producing tumor cells are not destroyed and histological samples are taken from amorphous paucicellular or even acellular components of the
tumor. This makes it impossible to grade the tumor or determine its type correctly.

Our series of patients was homogeneous for PMP resection (complete cytoreduction in all 36 patients) but not for the intraperitoneal chemotherapy protocol (several successive techniques and chemotherapy regimens). This situation resulted from the requirement for strictly controlled therapeutic trials to search for an optimal treatment. Nearly half of our patients treated between 1994 and 2001 were not given what was retrospectively considered optimal treatment. Five postoperative deaths resulted from a cerebral event and thus can be considered to be unrelated to the specific treatment studied here. Treatment-related mortality reported in the literature is to the order of 3-8% [18, 19], a rate similar to our experience over the last four years. Considering only complications requiring a specific invasive treatment [18], the postoperative morbidity in the present series was 27%. Indeed, operative morbidity and mortality are relatively high when curative treatment is attempted for patients with high-grade PMP. The chances of survival remain low for the same reason. Treatment is easier and complications less frequent for patients with minimally disseminated disease whose chances of survival are better [2, 3]. These observations emphasize the importance of diagnosing PMP early and of optimizing first-line treatment. Laparoscopy would be indicated for patients with an unexplained clinical or radiological presentation in order to establish the diagnosis of PMP as early as possible. If the diagnosis of PMP is certain, it would be inappropriate to undertake surgery for incomplete resection since the disease will continue to progress making a second intervention for the inevitable recurrence most difficult.

Two prognostic factors are of prime importance: completeness of the cytoreduction and tumor grade. The largest series reported to date [Sugarbaker [20, 21]] included 550 patients who underwent maximal surgery for complete cytoreduction followed by IPIC or HIIP. Complete cytoreduction (defined as tumor nodules < 2.5 mm in diameter remaining after surgery) was achieved in 79% of the patients. The 5-year survival rate was 20% (despite adjuvant IPIC or HIIP) among patients who had incomplete cytoreduction and continued to fall thereafter. This 5-year survival rate rose to 79% (P = 0.0001) and remained stable among patients who had complete cytoreduction. The overall 5-year survival rate for the 550 patients was only 53% after maximal surgery and IPIC or HIIC. This low rate points out the real gravity of PMP: more than half the patients die within 5 years [14, 16, 17, 20]. Median survival is only 2 years if resection is incomplete [18]. Partial surgery inevitably leads to a second operation (86% of the 56 patients in the Mayo Clinic series) [16]. Complete cytoreduction without intraperitoneal chemotherapy cannot prevent recurrence but can delay its onset (75% clinical recurrence at 2.6 years after complete cytoreduction versus 76% clinical recurrence at 1.9 years after incomplete cytoreduction) [16]. Perioperative intraperitoneal chemotherapy is designed to treat residual microscopic disease. Theoretically, HIIP is more efficacious than IPIC due to the added hyperthermic effect [22] and the fact that all surfaces are flushed when using the procedure considered by Sugarbaker [5, 20] and us as optimal. Strong scientific evidence is however lacking to prove that adjunction of IPIC or HIIP improves the prognosis in these patients [19]. Nevertheless, the extensive experience reported by Sugarbaker and the quality of the reported results are in favor of improved outcome with this type of treatment. Other reports of smaller series [8, 12, 15, 16, 23] and the results of the present study all point in the same direction, suggesting there is an agreement among experts on this question (strong agreement for grade 2 and 3 tumors, less strong agreement for grade 1 tumors). Consequently, it is currently advisable to propose this type of maximal treatment for all patients capable of tolerating it. Moreover, it would undoubtedly be advisable to propose a second-look during the next three years for all patients or in the event of clinical recurrence. Esquivel and Sugarbaker [24] have demonstrated that 5-year survival reached 74% among 98 patients who underwent a second operation but was only 68% among 223 patients who did not have a second operation.

The histological grade is also an important factor determining survival, as observed in our patients (figure 3) and as was clearly demonstrated by Sugarbaker in a larger series of patients who underwent complete cytoreductive surgery and IPIC or HIIP [20]. In that series, the 5-year survival was 80% among 224 patients with grade 1 PMP and 30% among 162 patients with grade 2 or 3 PMP (P = 0.0001). Histological grade is the only important prognostic factor after completeness of cytoreduction; dissemination in the peritoneal cavity only has a weak effect on prognosis.

In conclusion, in 2002, PMP remains a poorly understood clinical entity grouping together benign to more malignant disease forms with an overall 5-year survival (all types included) of less than 50%. The two principal prognostic factors are completeness of cytoreductive surgery and histological grade. In order to improve prognosis, complete cytoreductive surgery with HIIP should be proposed for patients with grade 2 or 3 tumors and perhaps for patients with grade 1 tumors. This major surgical protocol is easier to perform, better tolerated, and more effective when performed early.

REFERENCES


