

# Using CommonKADS to Build an Expertise Model for Breast Cancer Prognosis and Therapy

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- breast cancer: an Eastern Cooperative Oncology Group trial. *Cancer* 50(7): 1235-1244, 1982.
316. Smalley RV, Lefante J, Bartolucci A, et al.: A comparison of cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone (CMFVP) in patients with advanced breast cancer: a Southeastern Cancer Study Group project. *Breast Cancer Research and Treatment* 3(2): 209-220, 1983.
317. Tranum BL, McDonald B, Thigpen T, et al.: Adriamycin combinations in advanced breast cancer: a Southwest Oncology Group study. *Cancer* 49(5): 835-839, 1982.
318. Speyer JL, Green MD, Zeleniuch-Jacquotte A, et al.: ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. *Journal of Clinical Oncology* 10(1): 117-127, 1992.
319. Hortobagyi GN, Frye D, Buzdar AU, et al.: Decreased cardiac toxicity of doxorubicin administered by continuous intravenous infusion in combination chemotherapy for metastatic breast carcinoma. *Cancer* 63(1):37-45, 1989.
320. Rubens RD, Tinson CL, Coleman RE, et al.: Prednisolone improves the response to primary endocrine treatment for advanced breast cancer. *British Journal of Cancer* 58(5): 626-630, 1988.
321. Muss HB, Case LD, Capizzi RL, et al.: High- versus standard-dose megestrol acetate in women with advanced breast cancer: a phase III trial of the Piedmont Oncology Association. *Journal of Clinical Oncology* 8(11): 1797-1805, 1990.
322. Reichman BS, Seidman AD, Crown JP, et al.: Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *Journal of Clinical Oncology* 11(10): 1943-1951, 1993.
323. Chevallier B, Fumoleau P, Kerbrat P, et al.: Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Cooperative Group of the European Organization for Research and Treatment of Cancer. *Journal of Clinical Oncology* 13(2): 314-322, 1995.
324. Kennedy MJ, Beveridge RA, Rowley SD, et al.: High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intense induction as initial therapy for metastatic breast cancer. *Journal of the National Cancer Institute* 83(13): 920-926, 1991.
325. Antman K, Ayash L, Elias A, et al.: A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. *Journal of Clinical Oncology* 10(1): 102-110, 1992.
326. Stadtmauer EA, Eastern Cooperative Oncology Group: NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Comparison of Conventional CMF (CTX/MTX/5-FU) Maintenance vs High-Dose Chemotherapy with CTX/TSPA/CBDCA plus Autologous Bone Marrow and Peripheral Stem Cell Rescue in Women with Metastatic Breast Cancer Responding to Conventional Induction Chemotherapy (Summary Last Modified 05/95), E-PBT01, clinical trial, active, 11/01/90.

- treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. *Journal of Clinical Oncology* 10(6): 976-983, 1992.
300. Halverson KJ, Perez CA, Kuske RR, et al.: Isolated local-regional recurrence of breast cancer following mastectomy: radiotherapeutic management. *International Journal of Radiation Oncology, Biology, Physics* 19(4): 851-858, 1990.
301. Schwaibold F, Fowble BL, Solin LJ, et al.: The results of radiation therapy for isolated local regional recurrence after mastectomy. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 299-310, 1991.
302. Halverson KJ, Perez CA, Kuske RR, et al.: Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. *International Journal of Radiation Oncology, Biology, Physics* 23(2): 285-291, 1992.
303. Aberizk WJ, Silver B, Henderson IC, et al.: The use of radiotherapy for treatment of isolated locoregional recurrence of breast carcinoma after mastectomy. *Cancer* 58(6): 1214-1218, 1986.
304. Recht A, Hayes DF: Specific sites and emergencies: local recurrence. In: Harris Jr, Hellman S, Henderson IC, et al., Eds.: *Breast Diseases*. Philadelphia: J.B. Lippincott, 1987, pp 508-524.
305. Abner AL, Recht A, Eberlein T, et al.: Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. *Journal of Clinical Oncology* 11(1): 44-48, 1993.
306. Haffty BG, Fischer D, Rose M, et al.: Prognostic factors for local recurrence in the conservatively treated breast cancer patient: a cautious interpretation of the data. *Journal of Clinical Oncology* 9(6): 997-1003, 1991.
307. Haffty BG, Fischer D, Beinfield M, et al.: Prognosis following local recurrence in the conservatively treated breast cancer patient. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 293-298, 1991.
308. Ingle JN, Krook JE, Green SJ, et al.: Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. *Journal of Clinical Oncology* 4(2): 178-185, 1986.
309. Goldberg RM, Loprinzi CL, O'Fallon JR, et al.: Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *Journal of Clinical Oncology* 12(1): 155-158, 1994.
310. Kornblith AB, Hollis DR, Zuckerman E, et al.: Effect of megestrol acetate on quality of life in a dose-response trial in women with advanced breast cancer. *Journal of Clinical Oncology* 11(11): 2081-2089, 1993.
311. Cocconi G, Bisagni G, Ceci G, et al.: Low-dose aminoglutethimide with and without hydrocortisone replacement as a first-line endocrine treatment in advanced breast cancer: a prospective randomized trial of the Italian Oncology Group for Clinical Research. *Journal of Clinical Oncology* 10(6): 984-989, 1992.
312. Gale KE, Andersen JW, Tormey DC, et al.: Hormonal treatment for metastatic breast cancer: an Eastern Cooperative Oncology Group phase III trial comparing aminoglutethimide to tamoxifen. *Cancer* 73(2): 354-361, 1994.
313. Lanza LA, Natarajan G, Roth JA, et al.: Long-term survival after resection of pulmonary metastases from carcinoma of the breast. *Annals of Thoracic Surgery* 54(2): 244-248, 1992.
314. Howell A, Dodwell DJ, Anderson H, et al.: Response after withdrawal of tamoxifen and progestogens in advanced breast cancer. *Annals of Oncology* 3(8): 611-617, 1992.
315. Tormey DC, Gelman R, Band PR, et al.: Comparison of induction chemotherapies for metastatic

284. Taylor CW, Southwest Oncology Group: Phase III Randomized Comparison of Surgical Oophorectomy vs Medical Oophorectomy with ZDX in Premenopausal Patients with Metastatic ER-Positive or PgR-Positive Carcinoma of the Breast (Summary Last Modified 02/95), SWOG-8692, clinical trial, active, 08/01/87.
285. Ingle JN, Krook JE, Green SJ, et al.: Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. *Journal of Clinical Oncology* 4(2): 178-185, 1986.
286. Goldberg RM, Loprinzi CL, O'Fallon JR, et al.: Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *Journal of Clinical Oncology* 12(1): 155-158, 1994.
287. Tormey DC, Gelman R, Band PR, et al.: Comparison of induction chemotherapies for metastatic breast cancer: an Eastern Cooperative Oncology Group trial. *Cancer* 50(7): 1235-1244, 1982.
288. Smalley RV, Lefante J, Bartolucci A, et al.: A comparison of cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone (CMFVP) in patients with advanced breast cancer: a Southeastern Cancer Study Group project. *Breast Cancer Research and Treatment* 3(2): 209-220, 1983.
289. Tranum BL, McDonald B, Thigpen T, et al.: Adriamycin combinations in advanced breast cancer: a Southwest Oncology Group study. *Cancer* 49(5): 835-839, 1982.
290. Speyer JL, Green MD, Zeleniuch-Jacquotte A, et al.: ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. *Journal of Clinical Oncology* 10(1): 117-127, 1992.
291. Hortobagyi GN, Frye D, Buzdar AU, et al.: Decreased cardiac toxicity of doxorubicin administered by continuous intravenous infusion in combination chemotherapy for metastatic breast carcinoma. *Cancer* 63(1):37-45, 1989.
292. Rubens RD, Tinson CL, Coleman RE, et al.: Prednisolone improves the response to primary endocrine treatment for advanced breast cancer. *British Journal of Cancer* 58(5): 626-630, 1988.
293. Brandt SJ, Peters WP, Atwater SK, et al.: Effect of recombinant human granulocyte-macrophage colony-stimulating factor on hematopoietic reconstitution after high-dose chemotherapy and autologous bone marrow transplantation. *New England Journal of Medicine* 318(14): 869-876, 1988.
294. Perez JE, Machiavelli M, Leone BA, et al.: Ifosfamide and mitoxantrone as first-line chemotherapy for metastatic breast cancer. *Journal of Clinical Oncology* 11(3): 461-466, 1993.
295. Margolin KA, Doroshow JH, Akman SA, et al.: Effective initial therapy of advanced breast cancer with fluorouracil and high-dose, continuous infusion calcium leucovorin. *Journal of Clinical Oncology* 10(8): 1278-1283, 1992.
296. Lanza LA, Natarajan G, Roth JA, et al.: Long-term survival after resection of pulmonary metastases from carcinoma of the breast. *Annals of Thoracic Surgery* 54(2): 244-248, 1992.

#### **9.4.10. Inflammatory breast cancer**

297. Moore MP, Ihde JK, Crowe JP, et al.: Inflammatory breast cancer. *Archives of Surgery* 126(3): 304-306, 1991.

#### **9.4.11. Recurrent breast cancer**

298. Perry MC, Kardinal CG, Korzun AH, et al.: Chemohormonal therapy in advanced carcinoma of the breast: Cancer and Leukemia Group B protocol 8081. *Journal of Clinical Oncology* 5(10): 1534-1545, 1987.
299. Lichter AS, Lippman ME, Danforth DN, et al.: Mastectomy versus breast-conserving therapy in the

- tion with High-Dose CTX/TSPA plus Autologous Stem Cell Rescue in Women with Stage II/III Breast Cancer at High Risk of Recurrence (Summary Last Modified 12/94), EST-2190, clinical trial, active, 08/07/91.
271. Davidson NE, Eastern Cooperative Oncology Group: Phase III Randomized Comparison of Adjuvant Therapies in Premenopausal Women with Resected Node-Positive Hormone Receptor-Positive Adenocarcinoma of the Breast: CAF (CTX/DOX/5-FU) vs CAF Followed by ZDX vs CAF Followed by ZDX/TMX (Summary Last Modified 07/94), EST-5188, clinical trial, closed, 02/01/94.
272. Albain KS, Southwest Oncology Group: Phase III Randomized Comparison of Adjuvant Therapy with Tamoxifen (TMX) vs CAF (CTX/DOX/5-FU) plus Concurrent or Delayed TMX in Postmenopausal Women with Node- and Receptor-Positive Breast Cancer (Summary Last Modified 05/94), SWOG-8814, clinical trial, active, 05/15/89.
273. Bonadonna G, Veronesi U, Brambilla C, et al.: Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. *Journal of the National Cancer Institute* 82(19): 1539-1545, 1990.
274. Sener SF, Imperato JP, Khandekar JD, et al.: Achieving local control for inflammatory carcinoma of the breast. *Surgery, Gynecology and Obstetrics* 175(2): 141-144, 1992.
275. Moore MP, Ihde JK, Crowe JP, et al.: Inflammatory breast cancer. *Archives of Surgery* 126(3): 304-306, 1991.
276. Swain SM, Sorace RA, Bagley CS, et al.: Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. *Cancer Research* 47(14): 3889-3894, 1987.
277. Tormey DC, Gelman R, Band PR, et al.: Comparison of induction chemotherapies for metastatic breast cancer: an Eastern Cooperative Oncology Group trial. *Cancer* 50(7): 1235-1244, 1982.
278. Hortobagyi GN, Blumenschein GR, Spanos W, et al.: Multimodal treatment of locoregionally advanced breast cancer. *Cancer* 51(5): 763-768, 1983.
279. Perry MC, Kardinal CG, Korzun AH, et al.: Chemohormonal therapy in advanced carcinoma of the breast: Cancer and Leukemia Group B protocol 8081. *Journal of Clinical Oncology* 5(10): 1534-1545, 1987.

#### **9.4.9. Stage IV breast cancer**

280. Perry MC, Kardinal CG, Korzun AH, et al.: Chemohormonal therapy in advanced carcinoma of the breast: Cancer and Leukemia Group B protocol 8081. *Journal of Clinical Oncology* 5(10): 1534-1545, 1987.
281. Tannock IF: Treating the patient, not just the cancer. *New England Journal of Medicine* 317(24): 1534-1535, 1987.
282. Cleton FJ, van Holten-Verzantvoort AT, Bijvoet OL: Effect of long-term bisphosphonate treatment on morbidity due to bone metastases in breast cancer patients. *Recent Results in Cancer Research* 116: 73-78, 1989.
283. Livingston RB, Southwest Oncology Group: NCI HIGH PRIORITY CLINICAL TRIAL --- Phase III Randomized Comparison of Marrow Ablation with STAMP V (High-Dose CTX/TSPA/CDB-CA) and Autologous Stem Cell Rescue vs Standard Chemotherapy in Patients with Poor-Prognosis Advanced Breast Carcinoma (Summary Last Modified 08/93), SWOG-9115, clinical trial, closed, 01/01/94.

256. Tallman MS, Eastern Cooperative Oncology Group: NCI HIGH PRIORITY CLINICAL TRIAL - -- Phase III Study of Adjuvant CAF (CTX/DOX/5-FU) vs Adjuvant CAF Followed by Intensification with High-Dose CTX/TSPA plus Autologous Stem Cell Rescue in Women with Stage II/III Breast Cancer at High Risk of Recurrence (Summary Last Modified 12/94), EST-2190, clinical trial, active, 08/07/91.

257. Orel SG, Troupin RH, Patterson EA, et al.: Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. *Radiology* 183(1): 201-206, 1992.

#### 9.4.8. Stage III breast cancer

258. Tancini G, Bonadonna G, Valagussa P, et al.: Adjuvant CMF in breast cancer: comparative 5-year results of 12 versus 6 cycles. *Journal of Clinical Oncology* 1(1): 2-10, 1983.

259. Buzdar AU, Kau SW, Smith TL, et al.: Ten-year results of FAC adjuvant chemotherapy trial in breast cancer. *American Journal of Clinical Oncology* 12(2): 123-128, 1989.

260. Buzdar AU, Smith TL, Powell KC, et al.: Effect of timing of initiation of adjuvant chemotherapy on disease-free survival in breast cancer. *Breast Cancer Research and Treatment* 2(2): 163-169, 1982.

261. Fisher B, Redmond C, Fisher ER, et al.: A summary of findings from NSABP: trials of adjuvant therapy [Prior Annotation Incorrect]. In: Jones SE, Salmon SE, Eds.: *Adjuvant Therapy of Cancer IV*. New York: Grune and Stratton, Inc., 1984, pp 185-194.

262. Rivkin SE, Green S, Metch B, et al.: Adjuvant CMFVP versus melphalan for operable breast cancer with positive axillary nodes: 10-year results of a Southwest Oncology Group Study. *Journal of Clinical Oncology* 7(9): 1229-1238, 1989.

263. Fisher ER, Redmond C, Fisher B: Pathologic findings from the National Surgical Adjuvant Breast Project: VIII. Relationship of chemotherapeutic responsiveness to tumor differentiation. *Cancer* 51(2): 181-191, 1983.

264. Fisher B, Glass A, Redmond C, et al.: L-phenylalanine mustard (L-PAM) in the management of primary breast cancer: an update of earlier findings and a comparison with those utilizing L-PAM plus 5-fluorouracil (5-FU). *Cancer* 39(6, Suppl): 2883-2903, 1977.

265. Fisher B, Redmond C, Brown A, et al.: Influence of tumor estrogen and progesterone receptor levels on the response to tamoxifen and chemotherapy in primary breast cancer. *Journal of Clinical Oncology* 1(4): 227-241, 1983.

266. Goldberg RM, Loprinzi CL, O'Fallon JR, et al.: Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *Journal of Clinical Oncology* 12(1): 155-158, 1994.

267. Jones SE, Salmon SE, Allen H, et al.: Adjuvant treatment of node-positive breast cancer with Adriamycin-cyclophosphamide with or without radiation therapy: interim results of an ongoing clinical trial. *Recent Results in Cancer Research* 80: 162-169, 1982.

268. Speyer JL, Green MD, Kramer E, et al.: Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. *New England Journal of Medicine* 319(12): 745-752, 1988.

269. Hortobagyi GN, Frye D, Buzdar AU, et al.: Decreased cardiac toxicity of doxorubicin administered by continuous intravenous infusion in combination chemotherapy for metastatic breast carcinoma. *Cancer* 63(1):37-45, 1989.

270. Tallman MS, Eastern Cooperative Oncology Group: NCI HIGH PRIORITY CLINICAL TRIAL - -- Phase III Study of Adjuvant CAF (CTX/DOX/5-FU) vs Adjuvant CAF Followed by Intensifica-



- Clinical Oncology 7(9): 1229-1238, 1989.
243. Wood WC, Budman DR, Korzun AH, et al.: Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *New England Journal of Medicine* 330(18): 1253-1259, 1994.
244. Hryniuk W, Levine MN: Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. *Journal of Clinical Oncology* 4(8): 1162-1170, 1986.
245. Focan C, Andrien JM, Closon MT, et al.: Dose-response relationship of epirubicin-based first-line chemotherapy for advanced breast cancer: a prospective randomized trial. *Journal of Clinical Oncology* 11(7): 1253-1263, 1993.
246. Hryniuk WM: Average relative dose intensity and the impact on design of clinical trials. *Seminars in Oncology* 14(1): 65-74, 1987.
247. Speyer JL, Green MD, Kramer E, et al.: Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. *New England Journal of Medicine* 319(12): 745-752, 1988.
248. Hortobagyi GN, Frye D, Buzdar AU, et al.: Decreased cardiac toxicity of doxorubicin administered by continuous intravenous infusion in combination chemotherapy for metastatic breast carcinoma. *Cancer* 63(1):37-45, 1989.
249. Fisher B, Brown A, Wolmark N, et al.: Prolonging tamoxifen therapy for primary breast cancer: findings from the National Surgical Adjuvant Breast and Bowel Project clinical trial *Annals of Internal Medicine* 106(5): 649-654, 1987.
250. Cummings FJ, Gray R, Tormey DC, et al.: Adjuvant tamoxifen versus placebo in elderly women with node-positive breast cancer: long-term follow-up and causes of death. *Journal of Clinical Oncology* 11(1): 29-35, 1993.
251. Bonadonna G, Veronesi U, Brambilla C, et al.: Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. *Journal of the National Cancer Institute* 82(19): 1539-1545, 1990.
252. Tallman MS, Eastern Cooperative Oncology Group: NCI HIGH PRIORITY CLINICAL TRIAL -- Phase III Study of Adjuvant CAF (CTX/DOX/5-FU) vs Adjuvant CAF Followed by Intensification with High-Dose CTX/TSPA plus Autologous Stem Cell Rescue in Women with Stage II/III Breast Cancer at High Risk of Recurrence (Summary Last Modified 12/94), EST-2190, clinical trial, active, 08/07/91.
253. Davidson NE, Eastern Cooperative Oncology Group: Phase III Randomized Comparison of Adjuvant Therapies in Premenopausal Women with Resected Node-Positive Hormone Receptor-Positive Adenocarcinoma of the Breast: CAF (CTX/DOX/5-FU) vs CAF Followed by ZDX vs CAF Followed by ZDX/TMX (Summary Last Modified 07/94), EST-5188, clinical trial, closed, 02/01/94.
254. Albain KS, Southwest Oncology Group: Phase III Randomized Comparison of Adjuvant Therapy with Tamoxifen (TMX) vs CAF (CTX/DOX/5-FU) plus Concurrent or Delayed TMX in Postmenopausal Women with Node- and Receptor-Positive Breast Cancer (Summary Last Modified 05/94), SWOG-8814, clinical trial, active, 05/15/89.
255. Peters WP, Cancer and Leukemia Group B: NCI HIGH PRIORITY CLINICAL TRIAL--- Phase III Randomized Comparison of High-Dose CTX/CDDP/BCNU with Autologous Marrow and Peripheral Stem Cell Support vs Standard-Dose CTX/CDDP/BCNU Following Adjuvant CTX/DOX/5-FU in Women with Stage II/III Breast Cancer with at Least 10 Positive Axillary Nodes (Summary Last Modified 05/95), CLB-9082, clinical trial, active, 01/20/91.

- Journal of the National Cancer Institute 84(9): 683-689, 1992.
- 226.Recht A, Pierce SM, Abner A, et al.: Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. *Journal of Clinical Oncology* 9(6): 988-996, 1991.
- 227.Boice JD, Harvey EB, Blettner M, et al.: Cancer in the contralateral breast after radiotherapy for breast cancer. *New England Journal of Medicine* 326(12): 781-785, 1992.
- 228.Storm HH, Andersson M, Boice JD, et al.: Adjuvant radiotherapy and risk of contralateral breast cancer. *Journal of the National Cancer Institute* 84(16): 1245-1250, 1992.
- 229.Fraass BA, Roberson PL, Lichter AS: Dose to the contralateral breast due to primary breast irradiation. *International Journal of Radiation Oncology, Biology, Physics* 11(3): 485-497, 1985.
- 230.Kurtz JM, Amalric R, DeLouche G, et al.: The second ten years: Long-term risks of breast conservation in early breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 13(9): 1327-1332, 1987.
- 231.Fisher B, Redmond C, Fisher ER, et al.: Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *New England Journal of Medicine* 312(11): 674-681, 1985.
- 232.Martin JK, van Heerden JA, Taylor WF, et al.: Is modified radical mastectomy really equivalent to radical mastectomy in treatment of carcinoma of the breast? *Cancer* 57(3): 510-518, 1986.
- 233.Jones SE, Moon TE, Bonadonna G, et al.: Comparison of different trials of adjuvant chemotherapy in stage II breast cancer using a natural history data base. *American Journal of Clinical Oncology* 10(5): 387-395, 1987.
- 234.Tancini G, Bonadonna G, Valagussa P, et al.: Adjuvant CMF in breast cancer: comparative 5-year results of 12 versus 6 cycles. *Journal of Clinical Oncology* 1(1): 2-10, 1983.
- 235.Bonadonna G, Brusamolino E, Valagussa P, et al.: Combination chemotherapy as an adjuvant treatment in operable breast cancer. *New England Journal of Medicine* 294(8): 405-410, 1976.
- 236.Buzdar AU, Kau SW, Smith TL, et al.: Ten-year results of FAC adjuvant chemotherapy trial in breast cancer. *American Journal of Clinical Oncology* 12(2): 123-128, 1989.
- 237.Jones SE, Salmon SE, Allen H, et al.: Adjuvant treatment of node-positive breast cancer with Adriamycin-cyclophosphamide with or without radiation therapy: interim results of an ongoing clinical trial. *Recent Results in Cancer Research* 80: 162-169, 1982.
- 238.Fisher ER, Redmond C, Fisher B: Pathologic findings from the National Surgical Adjuvant Breast Project: VIII. Relationship of chemotherapeutic responsiveness to tumor differentiation *Cancer* 51(2): 181-191, 1983.
- 239.Fisher B, Glass A, Redmond C, et al.: L-phenylalanine mustard (L-PAM) in the management of primary breast cancer: an update of earlier findings and a comparison with those utilizing L-PAM plus 5-fluorouracil (5-FU). *Cancer* 39(6, Suppl): 2883-2903, 1977.
- 240.Fisher B, Redmond C, Brown A, et al.: Adjuvant chemotherapy with and without tamoxifen in the treatment of primary breast cancer: 5-year results from the National Surgical Adjuvant Breast and Bowel Project Trial. *Journal of Clinical Oncology* 4(4): 459-471, 1986.
- 241.Fisher B, Redmond C, Wickerham DL, et al.: Doxorubicin-containing regimens for the treatment of stage II breast cancer: the National Surgical Adjuvant Breast and Bowel Project experience. *Journal of Clinical Oncology* 7(5): 572-582, 1989.
- 242.Rivkin SE, Green S, Metch B, et al.: Adjuvant CMFVP versus melphalan for operable breast cancer with positive axillary nodes: 10-year results of a Southwest Oncology Group Study. *Journal of*

- 332(14): 907-911, 1995.
211. Sarrazin D, Le MG, Arriagada R, et al.: Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiotherapy and Oncology* 14(3): 177-184, 1989.
212. van Dongen JA, Bartelink H, Fentiman IS, et al.: Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *Journal of the National Cancer Institute Monograph* 11: 15-18, 1992.
213. Blichert-Toft M, Rose C, Andersen JA, et al.: Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *Journal of the National Cancer Institute Monograph* 11: 19-25, 1992.
214. Weiss MC, Fowble BL, Solin LJ, et al.: Outcome of conservative therapy for invasive breast cancer by histologic subtype. *International Journal of Radiation Oncology, Biology, Physics* 23(5): 941-947, 1992.
215. Fisher ER, Anderson S, Redmond C, et al.: Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. *Seminars in Surgical Oncology* 8(3): 161-166, 1992.
216. Solin LJ, Fowble BL, Schultz DJ, et al.: The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 279-287, 1991.
217. Schmidt-Ullrich R, Wazer DE, Tercilla O, et al.: Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 17(4): 733-738, 1989.
218. Wazer DE, DiPetrillo T, Schmidt-Ullrich R, et al.: Factors influencing cosmetic outcome and complication risk after conservative surgery and radiotherapy for early-stage breast carcinoma. *Journal of Clinical Oncology* 10(3): 356-363, 1992.
219. Holland R, Connolly JL, Gelman RS, et al.: The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. *Journal of Clinical Oncology* 8(1): 113-118, 1990.
220. Boyages J, Recht A, Connolly JL, et al.: Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiotherapy and Oncology* 19(1): 29-41, 1990.
221. Zafrani B, Vielh P, Fourquet A, et al.: Conservative treatment of early breast cancer: prognostic value of the ductal in situ component and other pathological variables on local control and survival. *European Journal of Cancer and Clinical Oncology* 25(11): 1645-1650, 1989.
222. Vicini, FA, Eberlein TJ, Connolly JL, et al.: The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. *Annals of Surgery* 214(3): 200-201, 1991.
223. Fowble B, Goodman RL, Glick JH, et al.: *Breast Cancer Treatment*. St. Louis, Mosby Year Book: 1991.
224. Liljegren G, Holmberg L, Adami HO, et al.: Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial: Uppsala-Orebro Breast Cancer Study Group. *Journal of the National Cancer Institute* 86(9): 717-722, 1994.
225. Clark RM, McCulloch PB, Levine MN, et al.: Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer.

- rence of new primary cancers. *Lancet* 1(8630): 117-120, 1989.
193. Magriples U, Naftolin F, Schwartz PE, et al.: High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *Journal of Clinical Oncology* 11(3): 485-490, 1993.
194. Fisher B, Costantino JP, Redmond CK, et al.: Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *Journal of the National Cancer Institute* 86(7): 527-537, 1994.
195. Fisher B, Redmond C, National Surgical Adjuvant Breast and Bowel Project: Systemic therapy in node-negative patients: updated findings from NSABP clinical trials [Prior Annotation Incorrect]. *Journal of the National Cancer Institute Monograph* 11: 105-116, 1992.
196. Barakat RR, Wong G, Curtin JP, et al.: Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. *Gynecologic Oncology* 55(2): 164-168, 1994.
197. Kedar RP, Bourne TH, Powles TJ, et al.: Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet* 343(8909): 1318-1321, 1994.
198. Neven P, De Muylder X, Van Belle Y, et al.: Tamoxifen and the uterus. *British Medical Journal* 309(6965): 1313-1314, 1994.
199. Love RR, Surawicz TS, Williams EC: Antithrombin III level, fibrinogen level, and platelet count changes with adjuvant tamoxifen therapy. *Archives of Internal Medicine* 152(2): 317-320, 1992.
200. Love RR, Cameron L, Connell BL, et al.: Symptoms associated with tamoxifen treatment in postmenopausal women. *Archives of Internal Medicine* 151(9): 1842-1847, 1991.
201. Goldberg RM, Loprinzi CL, O'Fallon JR, et al.: Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *Journal of Clinical Oncology* 12(1): 155-158, 1994.
202. Love RR, Wiebe DA, Newcomb PA, et al.: Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Annals of Internal Medicine* 115(11): 860-864, 1991.
203. McDonald CC, Stewart HJ: Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial. *British Medical Journal* 303(6800): 435-437, 1991.
204. Rutqvist LE, Mattsson A: Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. *Journal of the National Cancer Institute* 85(17): 1398-1406, 1993.
205. Love RR, Mazess RB, Barden HS, et al.: Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *New England Journal of Medicine* 326(13): 852-856, 1992.
206. Kristensen B, Ejlersen B, Dalgaard P, et al.: Tamoxifen and bone metabolism in postmenopausal low-risk breast cancer patients: a randomized study. *Journal of Clinical Oncology* 12(5): 992-997, 1994.
207. Love RR, Barden HS, Mazess RB, et al.: Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Archives of Internal Medicine* 154(22): 2585-2588, 1994.
208. Bentley CR, Davies G, Aclimandos WA: Tamoxifen retinopathy: a rare but serious complication. *British Medical Journal* 304(6825): 495-496, 1992.
209. Buzdar AU, Hortobagyi GN, Frye D, et al.: Bioequivalence of 20-mg once-daily tamoxifen relative to 10-mg twice-daily tamoxifen regimens for breast cancer. *Journal of Clinical Oncology* 12(1): 50-54, 1994.
210. Jacobson JA, Danforth DN, Cowan KH, et al.: Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *New England Journal of Medicine*

176. Taylor SG, Knuihan MW, Sleeper LA, et al.: Six-year results of the Eastern Cooperative Oncology Group trial of observation versus CMFP versus CMFPT in postmenopausal patients with node-positive breast cancer. *Journal of Clinical Oncology* 7(7): 879-889, 1989.
177. Pearson OH, Hubay CA, Gordon NH, et al.: Endocrine versus endocrine plus five-drug chemotherapy in postmenopausal women with stage II estrogen receptor-positive breast cancer. *Cancer* 64(9): 1819-1823, 1989.
178. The Ludwig Breast Cancer Study Group: Combination adjuvant chemotherapy for node-positive breast cancer: inadequacy of a single perioperative cycle. *New England Journal of Medicine* 319(11): 677-683, 1988.
179. Rosen PP, Groshen S, Kinne DW.: Prognosis in T2N0M0 stage I breast carcinoma: a 20-year follow-up study. *Journal of Clinical Oncology* 9(9): 1650-1661, 1991.
180. Bartlett K, Eremin O, Hutcheon A., et al.: Adjuvant tamoxifen in the management of operable breast cancer: The Scottish Trial. *Lancet* 2(8552): 171-175, 1987.
181. Bonadonna G, Valagussa P, Zambetti M, et al.: Milan adjuvant trials for stage I-II breast cancer. In: Salmon SE, Ed.: *Adjuvant Therapy of Cancer V*. New York: Grune and Stratton, Inc., 1987, pp 211-221.
182. National Institutes of Health Consensus Development Conference statement: adjuvant chemotherapy for breast cancer. *Journal of the American Medical Association* 254(24): 3461-3463, 1985.
183. Fisher B, Redmond C, Dimitrov NV, et al.: A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. *New England Journal of Medicine* 320(8): 473-478, 1989.
184. Fisher B, Costantino J, Redmond C, et al.: A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *New England Journal of Medicine* 320(8): 479-484, 1989.
185. Mansour EG, Gray R, Shatila AH, et al: Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer: an Intergroup study. *New England Journal of Medicine* 320(8): 485-490, 1989.
186. Bianco AR, De Placido S, Gall C, et al.: Adjuvant therapy with tamoxifen in operable breast cancer: 10 year results of the Naples (GUN) study. *Lancet* 2(8620): 1095-1099, 1988.
187. Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. *New England Journal of Medicine* 319(26): 1681-1692, 1988.
188. Reyno LM, Levine MN, Skingley P, et al.: Chemotherapy induced amenorrhoea in a randomised trial of adjuvant chemotherapy duration in breast cancer. *European Journal of Cancer* 29A(1): 21-23, 1993.
189. Scottish Cancer Trials Breast Group and ICRF Breast Unit, Guy's Hospital, London: Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. *Lancet* 341(8856): 1293-1298, 1993.
190. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339(8784): 1-15, 1992.
191. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339(8785): 71-85, 1992.
192. Fornander T, Cedermark B, Mattsson A, et al.: Adjuvant tamoxifen in early breast cancer: occur-

radical mastectomy in treatment of carcinoma of the breast? *Cancer* 57(3): 510-518, 1986.

#### 9.4.7. Stage II breast cancer

162. Fisher B, Fisher ER, Redmond C, et al.: Tumor nuclear grade, estrogen receptor, and progesterone receptor: their value alone or in combination as indicators of outcome following adjuvant therapy for breast cancer. *Breast Cancer Research and Treatment* 7(3): 147-160, 1986.
163. Fisher B, Redmond C, Poisson R, et al.: Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine* 320(13): 822-828, 1989.
164. Veronesi U, Luini A, Del Vecchio M, et al.: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *New England Journal of Medicine* 328(22): 1587-1591, 1993.
165. Veronesi U, Salvadori B, Luini A, et al.: Conservative treatment of early breast cancer: long-term results of 1232 cases treated with quadrantectomy, axillary dissection, and radiotherapy. *Annals of Surgery* 211(3): 250-259, 1990.
166. Fowble BL, Solin LJ, Schultz DJ, et al.: Ten year results of conservative surgery and irradiation for stage I and II breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 269-277, 1991.
167. Auquier A, Rutqvist LE, Host H, et al.: Post-mastectomy megavoltage radiotherapy: the Oslo and Stockholm trials. *European Journal of Cancer* 28(2-3): 433-437, 1992.
168. Velez-Garcia E, Carpenter JT, Moore M, et al.: Postsurgical adjuvant chemotherapy with or without radiotherapy in women with breast cancer and positive axillary nodes: a Southeastern Cancer Study Group (SEG) trial. *European Journal of Cancer* 28A(11): 1833-1837, 1992.
169. Pierce LJ, Glatstein E: Postmastectomy radiotherapy in the management of operable breast cancer. *Cancer* 74(1): 477-485, 1994.
170. Cuzick J, Stewart H, Rutqvist L, et al.: Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *Journal of Clinical Oncology* 12(3): 447-453, 1994.
171. Akhtar SS, Allan SG, Rodger A, et al.: A 10-year experience of tamoxifen as primary treatment of breast cancer in 100 elderly and frail patients. *European Journal of Surgical Oncology* 17(1): 30-35, 1991.
172. Gazet JC, Ford HT, Coombes RC, et al.: Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer. *European Journal of Surgical Oncology* 20(3): 207-214, 1994.
173. Fisher B, Brown AM, Dimitrov NV, et al.: Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the NSABP B-15. *Journal of Clinical Oncology* 8(9): 1483-1496, 1990.
174. Baum M, Brinkley DM, Dossett JA, et al.: Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer: analysis at eight years by Nolvadex Adjuvant Trial Organization. *British Journal of Cancer* 57(6): 608-611, 1988.
175. Fisher B, Redmond C, Legault-Poisson S, et al.: Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast and Bowel Project B-16. *Journal of Clinical Oncology* 8(6): 1005-1018, 1990.

144. Boyages J, Recht A, Connolly JL, et al.: Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiotherapy and Oncology* 19(1): 29-41, 1990.
145. Zafrani B, Vielh P, Fourquet A, et al.: Conservative treatment of early breast cancer: prognostic value of the ductal in situ component and other pathological variables on local control and survival. *European Journal of Cancer and Clinical Oncology* 25(11): 1645-1650, 1989.
146. Vicini, FA, Eberlein TJ, Connolly JL, et al.: The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. *Annals of Surgery* 214(3): 200-201, 1991.
147. Fowble B, Goodman RL, Glick JH, et al.: *Breast Cancer Treatment*. St. Louis, Mosby Year Book: 1991.
148. Veronesi U, Luini A, Del Vecchio M, et al.: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *New England Journal of Medicine* 328(22): 1587-1591, 1993.
149. Liljegren G, Holmberg L, Adami HO, et al.: Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial: Uppsala-Orebro Breast Cancer Study Group. *Journal of the National Cancer Institute* 86(9): 717-722, 1994.
150. Clark RM, McCulloch PB, Levine MN, et al.: Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *Journal of the National Cancer Institute* 84(9): 683-689, 1992.
151. Recht A, Pierce SM, Abner A, et al.: Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. *Journal of Clinical Oncology* 9(6): 988-996, 1991.
152. Auquier A, Rutqvist LE, Host H, et al.: Post-mastectomy megavoltage radiotherapy: the Oslo and Stockholm trials. *European Journal of Cancer* 28(2-3): 433-437, 1992.
153. Boice JD, Harvey EB, Blettner M, et al.: Cancer in the contralateral breast after radiotherapy for breast cancer. *New England Journal of Medicine* 326(12): 781-785, 1992.
154. Storm HH, Andersson M, Boice JD, et al.: Adjuvant radiotherapy and risk of contralateral breast cancer. *Journal of the National Cancer Institute* 84(16): 1245-1250, 1992.
155. Fraass BA, Roberson PL, Lichter AS: Dose to the contralateral breast due to primary breast irradiation. *International Journal of Radiation Oncology, Biology, Physics* 11(3): 485-497, 1985.
156. Inskip PD, Stovall M, Flannery JT: Lung cancer risk and radiation dose among women treated for breast cancer. *Journal of the National Cancer Institute* 86(13): 983-988, 1994.
157. Orel SG, Troupin RH, Patterson EA, et al.: Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. *Radiology* 183(1): 201-206, 1992.
158. Fowble BL, Solin LJ, Schultz DJ, et al.: Ten year results of conservative surgery and irradiation for stage I and II breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 269-277, 1991.
159. Kurtz JM, Amalric R, DeLouche G, et al.: The second ten years: Long-term risks of breast conservation in early breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 13(9): 1327-1332, 1987.
160. Fisher B, Redmond C, Fisher ER, et al.: Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *New England Journal of Medicine* 312(11): 674-681, 1985.
161. Martin JK, van Heerden JA, Taylor WF, et al.: Is modified radical mastectomy really equivalent to

128. Kristensen B, Ejlertsen B, Dalgaard P, et al.: Tamoxifen and bone metabolism in postmenopausal low-risk breast cancer patients: a randomized study. *Journal of Clinical Oncology* 12(5): 992-997, 1994.
129. Love RR, Barden HS, Mazess RB, et al.: Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years. *Archives of Internal Medicine* 154(22): 2585-2588, 1994.
130. Bentley CR, Davies G, Aclimandos WA: Tamoxifen retinopathy: a rare but serious complication. *British Medical Journal* 304(6825): 495-496, 1992.
131. Buzdar AU, Hortobagyi GN, Frye D, et al.: Bioequivalence of 20-mg once-daily tamoxifen relative to 10-mg twice-daily tamoxifen regimens for breast cancer. *Journal of Clinical Oncology* 12(1): 50-54, 1994.
132. Gazet JC, Ford HT, Coombes RC, et al.: Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer. *European Journal of Surgical Oncology* 20(3): 207-214, 1994.
133. Akhtar SS, Allan SG, Rodger A, et al.: A 10-year experience of tamoxifen as primary treatment of breast cancer in 100 elderly and frail patients. *European Journal of Surgical Oncology* 17(1): 30-35, 1991.
134. Dixon JM: Treatment of elderly patients with breast cancer. *British Medical Journal* 304(6833): 996-997, 1992.
135. Robertson JF, Ellis IO, Elston CW, et al.: Mastectomy or tamoxifen as initial therapy for operable breast cancer in elderly patients: 5-year follow-up. *European Journal of Cancer* 28A(4/5): 908-910, 1992.
136. Jacobson JA, Danforth DN, Cowan KH, et al.: Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *New England Journal of Medicine* 332(14): 907-911, 1995.
137. Veronesi U, Salvadori B, Luini A, et al.: Conservative treatment of early breast cancer: long-term results of 1232 cases treated with quadrantectomy, axillary dissection, and radiotherapy. *Annals of Surgery* 211(3): 250-259, 1990.
138. Schmidt-Ullrich R, Wazer DE, Tercilla O, et al.: Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 17(4): 733-738, 1989.
139. Weiss MC, Fowble BL, Solin LJ, et al.: Outcome of conservative therapy for invasive breast cancer by histologic subtype. *International Journal of Radiation Oncology, Biology, Physics* 23(5): 941-947, 1992.
140. Fisher ER, Anderson S, Redmond C, et al.: Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. *Seminars in Surgical Oncology* 8(3): 161-166, 1992.
141. Solin LJ, Fowble BL, Schultz DJ, et al.: The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 279-287, 1991.
142. Wazer DE, DiPetrillo T, Schmidt-Ullrich R, et al.: Factors influencing cosmetic outcome and complication risk after conservative surgery and radiotherapy for early-stage breast carcinoma. *Journal of Clinical Oncology* 10(3): 356-363, 1992.
143. Holland R, Connolly JL, Gelman RS, et al.: The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. *Journal of Clinical Oncology* 8(1): 113-118, 1990.



110. Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. *New England Journal of Medicine* 319(26): 1681-1692, 1988.
111. Reyno LM, Levine MN, Skingley P, et al.: Chemotherapy induced amenorrhoea in a randomised trial of adjuvant chemotherapy duration in breast cancer. *European Journal of Cancer* 29A(1): 21-23, 1993.
112. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339(8784): 1-15, 1992.
113. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339(8785): 71-85, 1992.
114. Fornander T, Cedermark B, Mattsson A, et al.: Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1(8630): 117-120, 1989.
115. Magriples U, Naftolin F, Schwartz PE, et al.: High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *Journal of Clinical Oncology* 11(3): 485-490, 1993.
116. Fisher B, Costantino JP, Redmond CK, et al.: Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *Journal of the National Cancer Institute* 86(7):527-537, 1994.
117. van Leeuwen FE, Benraadt J, Coebergh JW, et al.: Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 343(8895): 448-452, 1994.
118. Barakat RR, Wong G, Curtin JP, et al.: Tamoxifen use in breast cancer patients who subsequently develop corpus cancer is not associated with a higher incidence of adverse histologic features. *Gynecologic Oncology* 55(2): 164-168, 1994.
119. Kedar RP, Bourne TH, Powles TJ, et al.: Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet* 343(8909): 1318-1321, 1994.
120. Neven P, De Muylder X, Van Belle Y, et al.: Tamoxifen and the uterus. *British Medical Journal* 309(6965): 1313-1314, 1994.
121. Love RR, Surawicz TS, Williams EC: Antithrombin III level, fibrinogen level, and platelet count changes with adjuvant tamoxifen therapy. *Archives of Internal Medicine* 152(2): 317-320, 1992.
122. Love RR, Cameron L, Connell BL, et al.: Symptoms associated with tamoxifen treatment in postmenopausal women. *Archives of Internal Medicine* 151(9): 1842-1847, 1991.
123. Goldberg RM, Loprinzi CL, O'Fallon JR, et al.: Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *Journal of Clinical Oncology* 12(1): 155-158, 1994.
124. Love RR, Wiebe DA, Newcomb PA, et al.: Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Annals of Internal Medicine* 115(11): 860-864, 1991.
125. McDonald CC, Stewart HJ: Fatal myocardial infarction in the Scottish adjuvant tamoxifen trial. *British Medical Journal* 303(6800): 435-437, 1991.
126. Rutqvist LE, Mattsson A: Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. *Journal of the National Cancer Institute* 85(17): 1398-1406, 1993.
127. Love RR, Mazess RB, Barden HS, et al.: Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *New England Journal of Medicine* 326(13): 852-856, 1992.

- 577, 1991.
94. McGuire WL, Tandon AK, Allred DC, et al.: How to use prognostic factors in axillary node-negative breast cancer patients. *Journal of the National Cancer Institute* 82(12): 1006-1015, 1990.
  95. Fisher B, Redmond C, Wickerham DL, et al.: Systemic therapy in patients with node-negative breast cancer: a commentary based on two National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials. *Annals of Internal Medicine* 111(9): 703-712, 1989.
  96. Meyer JS: Cell kinetics in selection and stratification of patients for adjuvant therapy of breast carcinoma. *Journal of the National Cancer Institute Monograph* 1: 25-28, 1986.
  97. Sigurdsson H, Baldetorp B, Borg A, et al.: Indicators of prognosis in node-negative breast cancer. *New England Journal of Medicine* 322(15): 1045-1053, 1990.
  98. Rosen PP, Groshen S, Kinne DW: Survival and prognostic factors in node-negative breast cancer: long-term follow-up studies. *Journal of the National Cancer Institute Monograph* 11: 159-162, 1992.
  99. Stierer M, Rosen HR, Weber R, et al.: Long term analysis of factors influencing the outcome in carcinoma of the breast smaller than one centimeter. *Surgery, Gynecology and Obstetrics* 175(2): 151-160, 1992.
  100. Rosen PP, Groshen S, Kinne DW, et al.: Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. *Journal of Clinical Oncology* 11(11): 2090-2100, 1993.
  101. Baum M, Brinkley DM, Dossett JA, et al.: Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer: analysis at eight years by Nolvadex Adjuvant Trial Organization. *British Journal of Cancer* 57(6): 608-611, 1988.
  102. Bartlett K, Eremin O, Hutcheon A., et al.: Adjuvant tamoxifen in the management of operable breast cancer: The Scottish Trial. *Lancet* 2(8552): 171-175, 1987.
  103. Bonadonna G, Valagussa P, Zambetti M, et al.: Milan adjuvant trials for stage I-II breast cancer. In: Salmon SE, Ed.: *Adjuvant Therapy of Cancer V*. New York: Grune and Stratton, Inc., 1987, pp 211-221.
  104. National Institutes of Health Consensus Development Conference statement: adjuvant chemotherapy for breast cancer. *Journal of the American Medical Association* 254(24): 3461-3463, 1985.
  105. Fisher B, Redmond C, Dimitrov NV, et al.: A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors [Prior Annotation Incorrect]. *New England Journal of Medicine* 320(8): 473-478, 1989.
  106. Fisher B, Costantino J, Redmond C, et al.: A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *New England Journal of Medicine* 320(8): 479-484, 1989.
  107. Fisher B, Redmond C, National Surgical Adjuvant Breast and Bowel Project: Systemic therapy in node-negative patients: updated findings from NSABP clinical trials. *Journal of the National Cancer Institute Monograph* 11: 105-116, 1992.
  108. Mansour EG, Gray R, Shatila AH, et al: Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer: an Intergroup study. *New England Journal of Medicine* 320(8): 485-490, 1989.
  109. Bianco AR, De Placido S, Gall C, et al.: Adjuvant therapy with tamoxifen in operable breast cancer: 10 year results of the Naples (GUN) study. *Lancet* 2(8620): 1095-1099, 1988.

- an equal alternative? *Archives of Surgery* 126(4): 424-428, 1991.
79. Schnitt SJ, Silen W, Sadowsky NL, et al.: Ductal carcinoma in situ (intraductal carcinoma) of the breast. *New England Journal of Medicine* 318(14): 898-903, 1988.
  80. Solin LJ, Fowble BL, Yeh I, et al.: Microinvasive ductal carcinoma of the breast treated with breast-conserving surgery and definitive irradiation. *International Journal of Radiation Oncology, Biology, Physics* 23(5): 961-968, 1992.
  81. Walt AJ, Simon M, Swanson GM: The continuing dilemma of lobular carcinoma in situ. *Archives of Surgery* 127(8): 904-909, 1992.
  82. Paul Peter Rosen: Lobular Carcinoma In Situ and Intraductal Carcinoma of the Breast. In: McDivitt RW, Okerman MA, Ozzello L, et al., Eds.: *The Breast Book*. Baltimore: Williams and Wilkens, 1984, pp 59-105.
  83. Osborne MP, Hoda SA: Current management of lobular carcinoma in situ of the breast. *Oncology (Huntington NY)* 8(2): 45-49, 1994.

#### **9.4.6. Stage I breast cancer**

84. Rosen PP, Groshen S, Saigo PE, et al.: Pathological prognostic factors in stage I (T1 N0 M0) and stage II (T1 N1 M0) breast carcinoma: a study of 644 patients with median follow-up of 18 years. *Journal of Clinical Oncology* 7(9): 1239-1251, 1989.
85. Fisher B, Fisher ER, Redmond C, et al.: Tumor nuclear grade, estrogen receptor, and progesterone receptor: their value alone or in combination as indicators of outcome following adjuvant therapy for breast cancer. *Breast Cancer Research and Treatment* 7(3): 147-160, 1986.
86. Fisher B, Redmond C, Poisson R, et al.: Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine* 320(13): 822-828, 1989.
87. Blichert-Toft M, Rose C, Andersen JA, et al.: Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *Journal of the National Cancer Institute Monograph* 11: 19-25, 1992.
88. van Dongen JA, Bartelink H, Fentiman IS, et al.: Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *Journal of the National Cancer Institute Monograph* 11: 15-18, 1992.
89. Sarrazin D, Le MG, Arriagada R, et al.: Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. *Radiotherapy and Oncology* 14(3): 177-184, 1989.
90. Straus K, Lichter A, Lippman M, et al.: Results of the National Cancer Institute Early Breast Cancer Trial. *Journal of the National Cancer Institute Monograph* 11: 27-32, 1992.
91. Veronesi U, Banfi A, Salvadori B, et al.: Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomized trial. *European Journal of Cancer* 26(6): 668-670, 1990.
92. Graverson HP, Blichert-Toft M, Andersen JA, et al.: Breast cancer: risk of axillary recurrence in node-negative patients following partial dissection of the axilla. *European Journal of Surgical Oncology* 14(5): 407-412, 1988.
93. Barth RJ, Danforth DN, Venzon DJ, et al.: Level of axillary involvement by lymph node metastases from breast cancer is not an independent predictor of survival. *Archives of Surgery* 126(5): 574-

chives of *Internal Medicine* 153(23): 2638-2644, 1993.

61. Council on Scientific Affairs, American Medical Association: Silicone gel breast implants. *Journal of the American Medical Association* 270(21): 2602-2606, 1993.
62. Kessler DA, Merkatz RB, Schapiro R: A call for higher standards for breast implants. *Journal of the American Medical Association* 270(21): 2607-2608, 1993.

#### **9.4.5. Breast cancer in situ**

63. Ariel IM, Cleary JB, Eds.: *Breast Cancer - Diagnosis and Treatment*. New York: McGraw-Hill, 1987.
64. Patchefsky AS, Schwartz GF, Finkelstein SD, et al.: Heterogeneity of intraductal carcinoma of the breast. *Cancer* 63(4): 731-741, 1989.
65. Solin LJ, Fourquet A, McCormick B, et al.: Salvage treatment for local recurrence following breast-conserving surgery and definitive irradiation for ductal carcinoma in situ (intraductal carcinoma) of the breast. *International Journal of Radiation Oncology, Biology, Physics* 30(1): 3-9, 1994.
66. Solin LJ, Yeh I, Kurtz J, et al.: Ductal carcinoma in situ (intraductal carcinoma) of the breast treated with breast-conserving surgery and definitive irradiation. *Cancer* 71(8): 2532-2542, 1993.
67. Silverstein MJ, Gierson ED, Colburn WJ, et al.: Axillary lymphadenectomy for intraductal carcinoma of the breast. *Surgery, Gynecology and Obstetrics* 172(3): 211-214, 1991.
68. Schwartz GF: The role of excision and surveillance alone in subclinical DCIS of the breast. *Oncology (Huntington NY)* 8(2): 21-35, 1994.
69. Boice JD, Harvey EB, Blettner M, et al.: Cancer in the contralateral breast after radiotherapy for breast cancer. *New England Journal of Medicine* 326(12): 781-785, 1992.
70. Fraass BA, Roberson PL, Lichter AS: Dose to the contralateral breast due to primary breast irradiation. *International Journal of Radiation Oncology, Biology, Physics* 11(3): 485-497, 1985.
71. Orel SG, Troupin RH, Patterson EA, et al.: Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. *Radiology* 183(1): 201-206, 1992.
72. Frykberg ER, Santiago F, Betsill WL, et al.: Lobular carcinoma in situ of the breast. *Surgery, Gynecology and Obstetrics* 164(3): 285-301, 1987.
73. Ciatto S, Cataliotti L, Cardona G, et al.: Risk of infiltrating breast cancer subsequent to lobular carcinoma in situ. *Tumori* 78(4): 244-246, 1992.
74. Wolmark N, National Surgical Adjuvant Breast and Bowel Project: Randomized, Placebo-Controlled Clinical Trial to Determine the Worth of TMX for Preventing Breast Cancer (Summary Last Modified 11/94), NSABP-P-1, clinical trial, active, 04/16/92.
75. Stotter AT, McNeese M, Oswald MJ, et al.: The role of limited surgery with irradiation in primary treatment of ductal in situ breast cancer. *International Journal of Radiation Oncology, Biology, Physics* 18(2):283-287, 1990.
76. Bornstein BA, Recht A, Connolly JL, et al.: Results of treating ductal carcinoma in situ of the breast with conservative surgery and radiation therapy. *Cancer* 67(7): 7-13, 1991.
77. McCormick B, Rosen PP, Kinne D, et al.: Duct carcinoma in situ of the breast: an analysis of local control after conservation surgery and radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 289-292, 1991.
78. Silverstein MJ, Waisman JR, Gierson ED, et al.: Radiation therapy for intraductal carcinoma. Is it

- breast. *Journal of the American College of Surgeons* 178(2): 111-116, 1994.
45. Crowe JP, Gordon NH, Fry DE, et al.: Breast cancer survival and perioperative blood transfusion. *Surgery* 106(5): 836-841, 1989.
  46. Kieckbusch ME, O'Fallon JR, Ahmann DL, et al.: Blood transfusion exposure does not influence survival in patients with carcinoma of the breast. *Transfusion* 29(6): 500-504, 1989.
  47. The GIVIO Investigators: Impact of follow-up testing on survival and health-related quality of life in breast cancer patients: a multicenter randomized controlled trial. *Journal of the American Medical Association* 271(20): 1587-1592, 1994.
  48. Del Turco MR, Palli D, Cariddi A, et al.: Intensive diagnostic follow-up after treatment of primary breast cancer: a randomized trial. *Journal of the American Medical Association* 271(20): 1593-1597, 1994.
  49. Cobleigh MA, Berris RF, Bush T, et al.: Estrogen replacement therapy in breast cancer survivors - a time for change: Breast Cancer Committees of the Eastern Cooperative Oncology Group. *Journal of the American Medical Association* 272(7): 540-545, 1994.

#### **9.4.2. Cellular classification**

50. Breast. In: American Joint Committee on Cancer: Manual for Staging of Cancer. Philadelphia: JB Lippincott Company, 4th ed., 1992, pp 149-154.
51. Hawkins RE, Schofield JB, Fisher C, et al.: The clinical and histologic criteria that predict metastases from cystosarcoma phyllodes. *Cancer* 69(1): 141-147, 1992.
52. Ciatto S, Cataliotti L, Cardona G, et al.: Risk of infiltrating breast cancer subsequent to lobular carcinoma in situ. *Tumori* 78(4): 244-246, 1992.

#### **9.4.3. Stage information**

53. Breast. In: American Joint Committee on Cancer: Manual for Staging of Cancer. Philadelphia: JB Lippincott Company, 4th ed., 1992, pp 149-154.

#### **9.4.4. Treatment option overview**

54. Feller WF, Holt R, Spear S, et al.: Modified radical mastectomy with immediate breast reconstruction. *American Surgeon* 52(3): 129-133, 1986.
55. Cunningham BL: Breast reconstruction following mastectomy. In: Najarian JS, Delaney JP, Eds.: *Advances in Breast and Endocrine Surgery*. Chicago: Year Book Medical Publishers, 1986, pp 213-226.
56. Scanlon EF.: The role of reconstruction in breast cancer. *Cancer* 68(Suppl 5): 1144-1147, 1991.
57. Hang-Fu L, Snyderman RK.: State-of-the-art breast reconstruction. *Cancer* 68(Suppl 5): 1148-1156, 1991.
58. Council on Scientific Affairs, American Medical Association: Silicone gel breast implants. *Journal of the American Medical Association* 270(21): 2602-2606, 1993.
59. Kuske RR, Schuster R, Klein E, et al.: Radiotherapy and breast reconstruction: clinical results and dosimetry. *International Journal of Radiation Oncology, Biology, Physics* 21(2): 339-346, 1991.
60. Bridges AJ, Vasey FB: Silicone breast implants: history, safety, and potential complications. *Ar-*

- New England Journal of Medicine 322(15): 1045-1053, 1990.
27. Fisher B, Gunduz N, Constantino J, et al.: DNA flow cytometric analysis of primary operable breast cancer: relation of ploidy and s-phase fraction to outcome of patients in NSABP B-04. *Cancer* 68(5): 1465-1475, 1991.
  28. Wenger CR, Beardslee S, Owens MA, et al.: DNA ploidy, S-phase, and steroid receptors in more than 127,000 breast cancer patients. *Breast Cancer Research and Treatment* 28(1): 9-20, 1993.
  29. Allred DC, Clark GM, Tandon AK, et al.: HER-2/neu in node-negative breast cancer: prognostic significance of overexpression influenced by the presence of in situ carcinoma. *Journal of Clinical Oncology* 10(4): 599-605, 1992.
  30. Berns EM, Klijn JG, van Putten WL, et al.: c-myc amplification is a better prognostic factor than HER2/neu amplification in primary breast cancer. *Cancer Research* 52(5): 1107-1113, 1992.
  31. Paik S, Hazan R, Fisher ER, et al.: Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: prognostic significance of erbB-2 protein overexpression in primary breast cancer. *Journal of Clinical Oncology* 8(1): 103-112, 1990.
  32. Toikkanen S, Helin H, Isola J, et al.: Prognostic significance of HER-2 oncoprotein expression in breast cancer: a 30-year follow-up. *Journal of Clinical Oncology* 10(7): 1044-1048, 1992.
  33. Gusterson BA, Gelber RD, Goldhirsch A, et al.: Prognostic importance of c-erbB-2 expression in breast cancer. *Journal of Clinical Oncology* 10(7): 1049-1056, 1992.
  34. Gasparini G, Weidner N, Bevilacqua P, et al.: Tumor microvessel density, p53 expression, tumor size, and peritumoral lymphatic vessel invasion are relevant prognostic markers in node-negative breast carcinoma. *Journal of Clinical Oncology* 12(3): 454-466, 1994.
  35. Muss HB, Thor AD, Berry DA, et al.: c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. *New England Journal of Medicine* 330(8): 1260-1266, 1994.
  36. Veronesi U, Luini A, Mariani L, et al.: Effect of menstrual phase on surgical treatment of breast cancer. *Lancet* 343(8912): 1544-1546, 1994.
  37. Badwe RA, Gregory WM, Chaudary MA, et al.: Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. *Lancet* 337(8752): 1261-1264, 1991.
  38. Senie RT, Rosen PP, Rhodes P, et al.: Timing of breast cancer excision during the menstrual cycle influences duration of disease-free survival. *Annals of Internal Medicine* 115(5): 337-342, 1991.
  39. McGuire WL, Hilsenbeck S, Clark GM: Optimal mastectomy timing. *Journal of the National Cancer Institute* 84(5): 346-348, 1992.
  40. Gnant MF, Seifert M, Jakesz R, et al.: Breast cancer and timing of surgery during menstrual cycle: a 5-year analysis of 385 pre-menopausal women. *International Journal of Cancer* 52(5): 707-712, 1992.
  41. Nathan B, Bates T, Anbazhagan R, et al.: Timing of surgery for breast cancer in relation to the menstrual cycle and survival of premenopausal women. *British Journal of Surgery* 80(1): 43, 1993.
  42. de la Rochefordiere A, Asselain B, Scholl S, et al.: Simultaneous bilateral breast carcinomas: a retrospective review of 149 cases. *International Journal of Radiation Oncology, Biology, Physics* 30(1) 35-41, 1994.
  43. Orel SG, Troupin RH, Patterson EA, et al.: Breast cancer recurrence after lumpectomy and irradiation: role of mammography in detection. *Radiology* 183(1): 201-206, 1992.
  44. Gustafsson A, Tartter PI, Brower ST, et al.: Prognosis of patients with bilateral carcinoma of the

- BRCA2, to chromosome 13q12-13. *Science* 265(5181): 2088-2090, 1994.
10. Biesecker BB, Boehnke M, Calzone K, et al.: Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. *Journal of the American Medical Association* 269(15): 1970-1974, 1993.
  11. Hall JM, Lee MK, Newman B, et al.: Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250(4988): 1684-1689, 1990.
  12. Easton DF, Bishop DT, Ford D, et al.: Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *American Journal of Human Genetics* 52: 678-701, 1993.
  13. Fisher B, Fisher ER, Redmond C, et al.: Tumor nuclear grade, estrogen receptor, and progesterone receptor: their value alone or in combination as indicators of outcome following adjuvant therapy for breast cancer. *Breast Cancer Research and Treatment* 7(3): 147-160, 1986.
  14. Jensen EV, DeSombre ER: Steroid hormone binding and hormone receptors. In: Holland JF, Frei E, Bast RC, et al., Eds.: *Cancer Medicine*. Philadelphia: Lea & Febiger, 3rd ed., 1993, pp 815-823.
  15. Fisher B, Osborne CK, Margolese R, et al.: Neoplasms of the breast. In: Holland JF, Frei E, Bast RC, et al., Eds.: *Cancer Medicine*. Philadelphia: Lea & Febiger, 3rd ed., 1993, pp 1706-1716.
  16. Holmes FA, Fritsche HA, Loewy JW, et al.: Measurement of estrogen and progesterone receptors in human breast tumors: enzyme immunoassay versus binding assay. *Journal of Clinical Oncology* 8(6): 1025-1035, 1990.
  17. Fisher ER, Redmond C, Fisher B, et al.: Pathologic findings from the National Surgical Adjuvant Breast and Bowel Projects (NSABP): prognostic discriminants for 8-year survival for node-negative invasive breast cancer patients [Prior Annotation Incorrect]. *Cancer* 65(9, Suppl): 2121-2128, 1990.
  18. Cascinelli N, Greco M, Bufalino R, et al.: Prognosis of breast cancer with axillary node metastases after surgical treatment only. *European Journal of Cancer and Clinical Oncology* 23(6): 795-799, 1987.
  19. Moot SK, Peters GN, Cheek JH: Tumor hormone receptor status and recurrences in premenopausal node negative breast carcinoma. *Cancer* 60(3): 382-385, 1987.
  20. Rosen PP, Groshen S, Kinne DW.: Prognosis in T2N0M0 stage I breast carcinoma: a 20-year follow-up study. *Journal of Clinical Oncology* 9(9): 1650-1661, 1991.
  21. Tandon AK, Clark GM, Chamness GC, et al.: Cathepsin D and prognosis in breast cancer. *New England Journal of Medicine* 322(5): 297-302, 1990.
  22. Rosen PP, Groshen S, Kinne DW, et al.: Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. *Journal of Clinical Oncology* 11(11): 2090-2100, 1993.
  23. Davis BW, Gelber RD, Goldhirsch A, et al.: Prognostic significance of tumor grade in clinical trials of adjuvant therapy for breast cancer with axillary lymph node metastasis. *Cancer* 58(12): 2662-2670, 1986.
  24. International (Ludwig) Breast Cancer Study Group: Prognostic importance of occult axillary lymph node micrometastases from breast cancers. *Lancet* 335(8705): 1565-1568, 1990.
  25. Friedman S, Bertin F, Mouriessie H, et al.: Importance of tumor cells in axillary node sinus margins ('clandestine' metastases) discovered by serial sectioning in operable breast carcinoma. *Acta Oncologica* 27(5): 483-487, 1988.
  26. Sigurdsson H, Baldetorp B, Borg A, et al.: Indicators of prognosis in node-negative breast cancer.

ceedings of the 2nd Japanese Knowledge Acquisition for Knowledge-Based Systems Workshop, pages 23-42. Hitachi, Advanced Research Laboratory, Hatoyama, Saitama, Japan, 1992.

- B. J. Wielinga, W. Van de Velde, A. Th. Schreiber, and J. M. Akkermans. Towards a unification of knowledge modelling approaches. In Jean-Marc David, Jean-Paul Krivine, and Reid Simmons, editors, *Second Generation Expert Systems*, pages 299-335. Springer-Verlag, Berlin Heidelberg, Germany, 1993.
- B. J. Wielinga and A. Th. Schreiber. Reusable and shareable knowledge bases: A european perspective. In *Proceedings International Conference on Building and Sharing of Very Large-Scaled Knowledge Bases '93*, pages 103-115, Tokyo, Japan, December 1993. Japan Information Processing Development Center.
- F. van Harmelen and J. R. Balder. (ML)2: a formal language for KADS models of expertise. *Knowledge Acquisition Journal*, 4(1), 1992. Special issue: 'The KADS approach to knowledge engineering'.
- F. van Harmelen and J. Balder. (ML)2: a formal language for KADS models of expertise (short version). In *Proceedings of the Tenth European Conference on AI (ECAI'92)*, Vienna, Austria, August 1992.
- J. van den Elst, G. Schreiber, F. van Harmelen, and M. Thonnat. A functional specification of reusing software components. In *Proceedings of the 6th International Conference on Software Engineering and Knowledge Engineering, SEKE'94*, 1994.

## 9.4 Literature on breast cancer

### 9.4.1. Prognosis

1. Orel SG, Schnall MD, LiVolsi VA, et al.: Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. *Radiology* 190(2):485-493, 1994.
2. de la Rochefordiere A, Asselain B, Campana F, et al.: Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 341(8852): 1039-1043, 1993.
3. Gilchrist KW, Gray R, Fowble B, et al.: Tumor necrosis is a prognostic predictor for early recurrence and death in lymph node-positive breast cancer: a 10-year follow-up study of 728 Eastern Cooperative Oncology Group patients. *Journal of Clinical Oncology* 11(10): 1929-1935, 1993.
4. Bastarrachea J, Hortobagyi GN, Smith TL, et al.: Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. *Annals of Internal Medicine* 120(1): 18-25, 1994.
5. Elledge RM, Clark GM, Chamness GC, et al.: Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. *Journal of the National Cancer Institute* 86(9): 705-712, 1994.
6. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer: implications for risk prediction. *Cancer* 73(3): 643-651, 1994.
7. Gail MH, Brinton LA, Byar DP, et al.: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *Journal of the National Cancer Institute* 81(24): 1879-1886, 1989.
8. Miki Y, Swensen J, Shattuck-Eidens D, et al.: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 266(5182): 66-71, 1994.
9. Wooster R, Neuhausen SL, Mangion J, et al.: Localization of a breast cancer susceptibility gene,



- in Lecture Notes in Computer Science, pages 45-65, Berlin Heidelberg, Germany, September 1993. Springer-Verlag.
- J. Balder, F. van Harmelen, and M. Aben. A KADS/ML2 model of a scheduling task. In J. Treur and Th. Wetter, editors, Formal Specification of Complex Reasoning Systems, Workshop Series, pages 15-44. Ellis Horwood, 1993.
  - Joost Breuker. Modelling Artificial Legal Reasoning. In G. Boy, N. Aussenac, B. Gaines, and J. Boose, editors, Proceedings of the European workshop on Knowledge Acquisition, pages 34 - 45, Berlin, 1993. Springer Verlag.
  - Joost Breuker. Reusable Components for Artificial Problem Solvers: the Common KADS library experience. In C. Peyralbe, editor, Proceedings of the IJCAI-93 Workshop on Knowledge Sharing and Information Exchange, Paris, 1993. CAP. 14 p.
  - D. Fensel and F. van Harmelen. A comparison of languages which operationalise and formalise KADS models of expertise. The Knowledge Engineering Review, 1994.
  - A. Th. Schreiber, J. M. Akkermans, and B. J. Wielinga. On problems with the knowledge level perspective. In L. Steels and B. Smith, editors, AISB--91: Artificial Intelligence and Simulation of behaviour, pages 208-221, London, 1991. Springer-Verlag. Also in: Proceedings Banff'90 Knowledge Acquisition Workshop, J. H. Boose and B. R. Gaines (editors), SRDG Publications, University of Calgary, pages 30-1 - 30-14.
  - A. Th. Schreiber and B. J. Wielinga. Comparing KADS to conventional software engineering. In A. Th. Schreiber, B. J. Wielinga, and J. A. Breuker, editors, KADS: A Principled Approach to Knowledge-Based System Development, pages 151-165. Academic Press, London, 1993.
  - A. Th. Schreiber, P. Terpstra, P. Magni, and M. van Velzen. Analysing and implementing VT using COMMON-KADS. In A. Th. Schreiber and W. P. Birmingham, editors, Proceedings of the 8th Banff Knowledge Acquisition for Knowledge-Based Systems Workshop. Volume 3: Sisyphus II - - VT Elevator Design Problem, pages 44-1 -- 44-29, Alberta, Canada, January 1994. SRDG Publications, University of Calgary.
  - A. Th. Schreiber. Applying KADS to the office assignment domain. International Journal of Human-Computer Studies, 40(2), 1994. Special issue on Sisyphus 91/92 "Models of Problem Solving".
  - A. Th. Schreiber, B. J. Wielinga, J. M. Akkermans, W. Van de Velde, and A. Anjewierden. CML: The CommonKADS conceptual modelling language. In L. Steels, A. Th. Schreiber, and W. Van de Velde, editors, Proceedings European Knowledge Acquisition Workshop EKAW'94, volume 867 of Lecture Notes in Artificial Intelligence, pages 1-25, Berlin/Heidelberg, September 1994. Springer-Verlag.
  - A. Th. Schreiber, B. J. Wielinga, J. M. Akkermans, W. Van de Velde, and R. de Hoog. CommonKADS: A comprehensive methodology for KBS development. IEEE Expert, 9(6), December 1994.
  - A. Valente, J. Breuker, and B. Bredeweg. Integrating modeling approaches in the CommonKADS library. In A. Sloman, D. Hogg, G. Humphreys, A. Ramsay, and D. Partridge, editors, Prospects for Artificial Intelligence, Proceedings of the AISB'93, pages 121-130. IOS Press, Amsterdam, 1993.
  - A. Valente and C. Löckenhoff. Organization as guidance: A library of assessment models. In Proceedings of the Seventh European Knowledge Acquisition Workshop (EKAW'93), pages 243-262, 1993.
  - B. J. Wielinga, W. Van de Velde, A. Th. Schreiber, and J. M. Akkermans. The KADS knowledge modelling approach. In R. Mizoguchi, H. Motoda, J. Boose, B. Gaines, and R. Quinlan, editors, Pro-

- <http://www.pasteur.fr/welcome-fr.html>  
Institut Pasteur
- <http://www.med.nyu.edu/nih-guide.html>  
NIH GUIDE INDEX
- <http://cancer.med.upenn.edu/>  
OncoLink, The University of Pennsylvania Cancer Resource
- [http://wwwwic.nci.nih.gov/jnci/jnci\\_issues.html](http://wwwwic.nci.nih.gov/jnci/jnci_issues.html)  
Current JNCI issues available on-line

### 9.2.2. On Knowledge Acquisition

- <http://camis.stanford.edu/protege/>  
PROTÉGÉ's Home Page
- <http://arti.vub.ac.be/www/kads/welcome.html>  
CommonKADS in the VUB AI lab
- <ftp://swi.psy.uva.nl/pub/CommonKADS>  
Remote file [swi.psy.uva.nl/pub/CommonKADS](http://swi.psy.uva.nl/pub/CommonKADS)
- <http://www.swi.psy.uva.nl/projects/Kactus/toolkit/about.html>  
About the KACTUS toolkit
- <file://localhost/u/samy/0/acacia/commun/hyperdoc/html/Home.html>  
Home HyperDoc

## 9.3 Literature on CommonKADS

- M. Aben. Formally specifying re-usable knowledge model components. *Knowledge Acquisition Journal*, 5:119-141, 1993.
- M. Aben, Y. Shahr, and M.A. Musen. Temporal abstraction mechanisms as kads inferences. In Brian Gaines and Mark Musen, editors, *Proceedings of the 8th Banff Knowledge Acquisition for Knowledge-based Systems Workshop*, pages 28-1 - 28-22, February 1994.
- J. M. Akkermans, F. van Harmelen, A. Th. Schreiber, and B. J. Wielinga. A formalisation of knowledge-level models for knowledge acquisition. *International Journal of Intelligent Systems*, 8(2):169-208, 1993. Reprinted in: K. M. Ford and J. M. Bradshaw, eds. (1993), *Knowledge Acquisition as Modelling*, New York, Wiley.
- J. M. Akkermans, B. J. Wielinga, and A. Th. Schreiber. Steps in constructing problem-solving methods. In N. Aussenac, G. Boy, B. Gaines, M. Linster,
- J.-G. Ganascia, and Y. Kodratoff, editors, *Knowledge Acquisition for Knowledge-Based Systems. Proceedings of the 7th European Workshop EKAW'93*, Toulouse and Caylus, France, number 723

## 9 Appendix D: further references

The references which are reported here have been divided in different subsections. The first subsection refers to the courses attended during this visiting period; the second subsection refers to a selection of WWW sites which have been frequently accessed during this work. Finally, the other two subsections refer to a greater list of references on CommonKADS and on breast cancer prognosis and treatment which might be useful for readers interested in this field.

### 9.1 Attended courses and publication produced in relation to this work

European School of Oncology - Advanced Course: Breast Cancer, 2nd-4th October, 1995, Milan, Italy. Chairman of the Scientific Committee Prof. U. Veronesi. Chairman of the Course/Seminar Prof. J-Y. Petit, Dr. D.W. Kinne.

Sacile, R., Ruggiero, C., Dieng, R., Applicazione ed uso di CommonKADS per creare un modello concettuale per la prognosi del tumore della mammella. Congresso Annuale Aica (Associazione Italiana per l'Informatica ed il Calcolo Automatico), vol.2, pp. 691-696.

### 9.2 List of WWW server

#### 9.2.1. On Cancer Information

- <http://golgi.harvard.edu/biopages/medicine.html>  
The World-Wide Web Virtual Library: Biosciences - Medicine
- <http://nysernet.org/bcic/>  
Breast Cancer Information
- <gopher://gopher.ncc.go.jp/>  
National Cancer Center, Tokyo JAPAN
- <http://galaxy.einet.net/galaxy/Medicine/Medical-Specialties/Cancer.html>  
Cancer (Medical Specialties)
- <gopher://gan1.ncc.go.jp/11/CNET/Physicians>  
For Physicians
- <http://biomed.nus.sg/Cancer/welcome.html>  
CancerNet

```
    type : primitive ;
    sub-tasks : cover ;
    control-structure :
    generate(c:initial_complaint -> h:hypothesis) =
        cover(c:initial_complaint -> h:hypothesis) ;

task test ;
task-definition
    goal : «test the risk» ;
    input : initial_complaint : «risk value» ;
    output : hypothesis : «risk value» ;
task-body
    type : primitive ;
    sub-tasks : match ;
    control-structure :
    test(c:risk1 -> h:risk2) =
        match(c:risk1 -> h:risk2);
```

```
--inference establish
  --operation-type : backwardall ;
  --input-roles : initial_complaint -> state ;
  --output-roles : hypothesis -> state ;
  --static-roles : necessary_condition -> cause in
causal_model ;
  --specification : «une» ;

task-knowledge

task bc_prognosis ;
task-definition
  goal : «define the bc risk» ;
  input : initial_complaint : «a» ; biol_manifestation :
«b» ;
  output : prognosis : «c» ;
  specification : «assess the bc risk, confirm by addi-
tional biol_manifestation» ;
task-body
  type : primitive ;
  sub-tasks : generate_biol , generate ;
  additional-roles : hypothesis : «» ;
  control-structure :
  bc_prognosis(c:initial_complaint, m:biol_manifestation
-> h:prognosis) =
    generate_biol(m:biol_manifestation -> d:complaint) ;
    generate(d:complaint -> h1:hypothesis) ;
    generate(c:initial_complaint -> h2:hypothesis) ;
    test(h1:hypothesis -> h: prognosis);
    test(h2:hypothesis -> h: prognosis);

task generate_biol ;
task-definition
  goal : «generate a biol risk fact» ;
  input : initial_complaint : «» ;
  output : hypothesis : «» ;
task-body
  type : primitive ;
  sub-tasks : cover ;
  control-structure :
  generate(c:initial_complaint -> h:hypothesis) =
    cover_biol(c:initial_complaint -> h:hypothesis) ;

task generate ;
task-definition
  goal : «generate a possible risk» ;
  input : initial_complaint : «» ;
  output : hypothesis : «» ;
task-body
```

---

```

status of Thymidine_labeling_index = high

status of Proliferative_capacity = low
has_biol_manifestation
status of S_phase_fraction = low

status of Proliferative_capacity = high
has_biol_manifestation
status of S_phase_fraction = high

status of Proliferative_capacity = high
has_biol_manifestation
status of S_phase_fraction = medium
;

domain-model : risk_model ; uses : breast_cancer ;
rules :

status of final_risk = high
caused_by_risk
status of risk = high

status of final_risk = low
caused_by_risk
status of risk = low
;

inference-knowledge

inference cover
  operation-type : backward ;
  input-roles : initial_complaint -> state ;
  output-roles : hypothesis -> state ;
  static-roles : potential_cause -> caused_by in
causal_model;
  specification : «any» ;

inference cover_biol
  operation-type : backward ;
  input-roles : initial_complaint -> state ;
  output-roles : hypothesis -> state ;
  static-roles : biol_cause -> has_biol_manifestation in
behavioral_model;
  specification : «any» ;

inference match
  operation-type : backward;
  input-roles : risk1 -> state ;
  output-roles : risk2 -> state ;
  static-roles : produce -> caused_by_risk in risk_model;
  specification : «any» ;

```

```
relation has_biol_manifestation ;
    argument-1 : state ;
        argument-role : cause ;
    argument-2 : biol_manifestation ;
        argument-role : effect ;

relation caused_by_risk;
    argument-1 : state ;
        argument-role : cause ;
    argument-2 : state ;
        argument-role : effect ;

domain-model : causal_model ; uses : breast_cancer ;
--status of Size = little and--status of axillary_nodes =
negative and--status of ER = positive and--status of
Proliferative_capacity = low--cause--status of risk = low
rules :

status of risk = high
caused_by
status of Size = big

status of risk = high
caused_by
status of axillary_nodes = positive

status of risk = high
caused_by
status of ER = negative

status of risk = high
caused_by
status of Proliferative_capacity = high
;

domain-model : behavioral_model ; uses : breast_cancer ;
rules :

status of Proliferative_capacity = low
has_biol_manifestation
status of Ploidy = aneuploid

status of Proliferative_capacity = high
has_biol_manifestation
status of Ploidy = diploid

status of Proliferative_capacity = low
has_biol_manifestation
status of Thymidine_labeling_index = low

status of Proliferative_capacity = high
has_biol_manifestation
```

```

        status : {low, high} ;
state_variable(Primary_tumor_prognostic_factor) ;
        differentiation-of

concept Thymidine_labeling_index ;
    sub-type-of : Primary_tumor_prognostic_factor ;
    properties :
        status : {low, high} ;
        differentiation-of
observable_variable(Primary_tumor_prognostic_factor) ;

concept S_phase_fraction ;
    sub-type-of : Primary_tumor_prognostic_factor ;
    properties :
        status : {low, medium, high} ;
        differentiation-of
observable_variable(Primary_tumor_prognostic_factor) ;

concept Ploidy ;
    sub-type-of : Primary_tumor_prognostic_factor ;
    properties :
        status : {diploid, aneuploid} ;
        differentiation-of
observable_variable(Primary_tumor_prognostic_factor) ;

expression state ;
    description : «status of Size = big» ;
        operand      :      state_variable      of
Primary_tumor_prognostic_factor ;

expression biol_manifestation ;
        operand      :      observable_variable      of
Primary_tumor_prognostic_factor ;

expression risk_factor ;
description : «status of risk = high» ;
operand : status of risk;

relation cause ;
    inverse : caused_by ;
    argument-1 : state ;
        argument-role : cause ;
    argument-2 : state ;
        argument-role : effect ;

relation caused_by ;
    inverse : cause ;
    argument-1 : state ;
        argument-role : cause ;
    argument-2 : state ;
        argument-role : effect ;

```



## 8 Appendix C: a simple CommonKADS model for breast cancer therapy

```
expertise-model BcPrognosis ;

domain-knowledge
ontology breast_cancer ;
definitions :
concept Primary_tumor_prognostic_factor ;
  properties :
    observable_variable : universal ;
    state_variable : universal ;

concept risk ;
  sub-type-of : Primary_tumor_prognostic_factor ;
  properties :
    status : {high, low} ;
    state_variable : differentiation-of
      (Primary_tumor_prognostic_factor) ;

concept final_risk ;
  sub-type-of : Primary_tumor_prognostic_factor ;
  properties :
    status : {high, low} ;
    state_variable : differentiation-of
      (Primary_tumor_prognostic_factor) ;

concept Size ;
  sub-type-of : Primary_tumor_prognostic_factor ;
  properties :
    status : {big, little} ;
    state_variable : differentiation-of
      (Primary_tumor_prognostic_factor) ;

concept axillary_nodes ;
  sub-type-of : Primary_tumor_prognostic_factor ;
  properties :
    status : {positive, negative} ;
    state_variable : differentiation-of
      (Primary_tumor_prognostic_factor) ;

concept ER ;
  sub-type-of : Primary_tumor_prognostic_factor ;
  properties :
    status : {positive, negative} ;
    state_variable : differentiation-of
      (Primary_tumor_prognostic_factor) ;

concept Proliferative_capacity ;
  sub-type-of : Primary_tumor_prognostic_factor ;
  properties :
```

```
ARGUMENT2 :CONCEPT Size
AXIOMS :
axiom 1 :IF Size(level) = [0-1]
        THEN Positive axillary nodes(level) = 20
axiom 2 :IF Size(level) = [1-2.9]
        THEN Positive axillary nodes(level) = 39
axiom 3 :IF Size(level) = [2.9-infinite]
        THEN Positive axillary nodes(level) = 69
END RELATION (Positive axillary nodes) depend from (Size)
```

Relation

```

                                [Size(level) = unknown]
ND RELATION (Size) depend from (S-phase fraction)

Relation

*

RELATION (Positive axillary nodes) depend from (Ploidy)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Positive axillary nodes
  ARGUMENT2    :CONCEPT Ploidy
  AXIOMS       :
  axiom 1      :IF Ploidy(status)=diploid
                THEN {with probability=0.64}
                [Positive axillary nodes(status) = null]
                OR {with probability=0.36}
                [Positive axillary nodes(status) = low/high]
  axiom 2      :IF Ploidy(status)=aneuploid
                THEN {with probability=0.59}
                [Positive axillary nodes(status) = null]
                OR {with probability=0.41}
                [Positive axillary nodes(status) = low/high]
END RELATION (Positive axillary nodes) depend from (Ploidy)

Relation

*

RELATION (Positive axillary nodes) depend from (S-phase fraction)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Positive axillary nodes
  ARGUMENT2    :CONCEPT S-phase fraction
  AXIOMS       :
  axiom 1      :IF S-phase fraction(status)=low
                THEN {with probability=0.65}
                [Positive axillary nodes(status) = null]
                OR {with probability=0.35}
                [Positive axillary nodes(status) = low/high]
  axiom 2      :IF S-phase fraction(status)=high
                THEN {with probability=0.58}
                [Positive axillary nodes(status) = null]
                OR {with probability=0.42}
                [Positive axillary nodes(status) = low/high]
END RELATION (Positive axillary nodes) depend from (S-phase fraction)

*

RELATION (Positive axillary nodes) depend from (Size)
  SOURCES      :Neoplasie della mammella(622)
  ARGUMENT1    :CONCEPT Positive axillary nodes
```

```

RELATION (Size) depend from (Ploidy)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Size
  ARGUMENT2    :CONCEPT Ploidy
  AXIOMS       :
  axiom 1      :IF Ploidy(status)=diploid
                THEN {with probability=0.34}
                [Size(level) = [0-2]
                OR {with probability=0.41}
                [Size(level) = [2-4]
                OR {with probability=0.24}
                [Size(level) = [4-infinite]
                OR {with probability=0.1}
                [Size(level) = unknown]
  axiom 2      :IF Ploidy(status)=aneuploid
                THEN {with probability=0.23}
                [Size(level) = [0-2]]
                OR {with probability=0.44}
                [Size(level) = [2-4]]
                OR {with probability=0.32}
                [Size(level) = [4-infinite]]
                OR {with probability=0.1}
                [Size(level) = unknown]
END RELATION (Size) depend from (Ploidy)

```

Relation

\*

```

RELATION (Size) depend from (S-phase fraction)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Size
  ARGUMENT2    :CONCEPT S-phase fraction
  AXIOMS       :
  axiom 1      :IF S-phase fraction(status)=low
                THEN {with probability=0.32}
                [Size(level) = [0-2]
                OR {with probability=0.44}
                [Size(level) = [2-4]
                OR {with probability=0.23}
                [Size(level) = [4-infinite]
                OR {with probability=0.1}
                [Size(level) = unknown]
  axiom 2      :IF S-phase fraction(status)=high
                THEN {with probability=0.25}
                [Size(level) = [0-2]
                OR {with probability=0.43}
                [Size(level) = [2-4]
                OR {with probability=0.32}
                [Size(level) = [4-infinite]
                OR {with probability=0}

```

```
RELATION (Nuclear grade) depend from (Ploidy)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Nuclear grade
  ARGUMENT2    :CONCEPT Ploidy
  AXIOMS       :
  axiom 1      :IF Ploidy(status)=diploid
                THEN {with probability=0.27}
                  [Nuclear grade(status) = poor]
                  OR {with probability=0.72}
                  [Nuclear grade(status) = good]
                  OR {with probability=0.1}
                  [Nuclear grade(status) = unknown]
  axiom 2      :IF Ploidy(status)=aneuploid
                THEN {with probability=0.44}
                  [Nuclear grade(status) = poor]
                  OR {with probability=0.55}
                  [Nuclear grade(status) = good]
                  OR {with probability=0.1}
                  [Nuclear grade(status) = unknown]
END RELATION (Nuclear grade) depend from (Ploidy)
```

Relation

\*

```
RELATION (Nuclear grade) depend from (S-phase fraction)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Nuclear grade
  ARGUMENT2    :CONCEPT S-phase fraction
  AXIOMS       :
  axiom 1      :IF S-phase fraction(status)=low
                THEN {with probability=0.28}
                  [Nuclear grade(status) = poor]
                  OR {with probability=0.71}
                  [Nuclear grade(status) = good]
                  OR {with probability=0.1}
                  [Nuclear grade(status) = unknown]
  axiom 2      :IF S-phase fraction(status)=high
                THEN {with probability=0.45}
                  [Nuclear grade(status) = poor]
                  OR {with probability=0.54}
                  [Nuclear grade(status) = good]
                  OR {with probability=0.1}
                  [Nuclear grade(status) = unknown]
END RELATION (Nuclear grade) depend from (S-phase frac-
tion)
```

Relation

\*

```

                                OR {with probability=0.44}
                                [Grading(status) = 3]
END RELATION (Grading) depend from(ER)

```

Relation

```

*

RELATION (Age) depend from (Ploidy)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Age
  ARGUMENT2    :CONCEPT Ploidy
  AXIOMS       :
  axiom 1      :IF Ploidy(status)=diploid
                THEN {with probability=0.3}
                [Age(level) = [0-49]]
                OR {with probability=0.7}
                [Age(level) = [50-150]]
  axiom 2      :IF Ploidy(status)=aneuploid
                THEN {with probability=0.33}
                [Age(level) = [0-49]]
                OR {with probability=0.67}
                [Age(level) = [50-150]]
END RELATION (Age) depend from (Ploidy)

```

Relation

```

*

RELATION (Age) depend from (S-phase fraction)
  SOURCES      :Cancer 68:(1469)
  ARGUMENT1    :CONCEPT Age
  ARGUMENT2    :CONCEPT S-phase fraction
  AXIOMS       :
  axiom 1      :IF S-phase fraction(status)=low
                THEN {with probability=0.31}
                [Age(level) = [0-49]]
                OR {with probability=0.69}
                [Age(level) = [50-150]]
  axiom 2      :IF S-phase fraction(status)=high
                THEN {with probability=0.33}
                [Age(level) = [0-49]]
                OR {with probability=0.67}
                [Age(level) = [50-150]]
END RELATION (Age) depend from (S-phase fraction)

```

Relation

\*

```
Relation

*

RELATION (Grading) depend from (Peritumoral lymphatic
vessel invasion)
  SOURCES      :Cancer 58:(2665)
  ARGUMENT1    :CONCEPT Grading
  ARGUMENT2    :CONCEPT Peritumoral lymphatic vessel in-
vasion
  AXIOMS       :
    axiom 1    :IF Peritumoral lymphatic vessel inva-
sion(status)=Positive
                THEN {with probability=0.28}
                [Grading(status) = 1]
                OR {with probability=0.48}
                [Grading(status) = 2]
                OR {with probability=0.24}
                [Grading(status) = 3]
    axiom 2    :IF Peritumoral lymphatic vessel inva-
sion(status)=negative
                THEN {with probability=0.18}
                [Grading(status) = 1]
                OR {with probability=0.49}
                [Grading(status) = 2]
                OR {with probability=0.33}
                [Grading(status) = 3]
  END RELATION (Grading) depend from (Peritumoral lymphat-
ic vessel invasion)
```

```
Relation

*

RELATION (Grading) depend from(ER)
  SOURCES      :Cancer 58:(2665)
  ARGUMENT1    :CONCEPT Grading
  ARGUMENT2    :CONCEPT ER
  AXIOMS       :
    axiom 1    :IF ER(status)=Positive
                THEN {with probability=0.29}
                [Grading(status) = 1]
                OR {with probability=0.52}
                [Grading(status) = 2]
                OR {with probability=0.19}
                [Grading(status) = 3]
    axiom 2    :IF ER(status)=negative
                THEN {with probability=0.12}
                [Grading(status) = 1]
                OR {with probability=0.44}
                [Grading(status) = 2]
```

node)

Relation

\*

```

RELATION (Grading) depend from (Menopause)
  SOURCES      :Cancer 58:(2665)
  ARGUMENT1    :CONCEPT Grading
  ARGUMENT2    :CONCEPT Menopause
  AXIOMS       :
  axiom 1      :IF Menopause(status)=pre
                THEN {with probability=0.21}
                [Grading(status) = 1]
                OR {with probability=0.48}
                [Grading(status) = 2]
                OR {with probability=0.31}
                [Grading(status) = 3]
  axiom 2      :IF Menopause(status)=post
                THEN {with probability=0.24}
                [Grading(status) = 1]
                OR {with probability=0.50}
                [Grading(status) = 2]
                OR {with probability=0.26}
                [Grading(status) = 3]
END RELATION (Grading) depend from (Menopause)

```

Relation

\*

```

RELATION (Grading) depend from (Size)
  SOURCES      :Cancer 58:(2665)
  ARGUMENT1    :CONCEPT Grading
  ARGUMENT2    :CONCEPT Size
  AXIOMS       :
  axiom 1      :IF Size(status)=T1
                THEN {with probability=0.28}
                [Grading(status) = 1]
                OR {with probability=0.47}
                [Grading(status) = 2]
                OR {with probability=0.25}
                [Grading(status) = 3]
  axiom 2      :IF Size(status)=T2-3
                THEN {with probability=0.18}
                [Grading(status) = 1]
                OR {with probability=0.50}
                [Grading(status) = 2]
                OR {with probability=0.32}
                [Grading(status) = 3]
END RELATION (Grading) depend from (Size)

```



```

        [Size(status) = T0-1]
        OR {with probability=0.46}
        [Size(status) = T2]
        OR {with probability=0.22}
        [Size(status) = T3]
        OR {with probability=0.6}
        [Size(status) = T4]
    axiom 2 :IF Age(level)=[34-40]
    THEN {with probability=0.34}
    [Size(status) = T0-1]
    OR {with probability=0.44}
    [Size(status) = T2]
    OR {with probability=0.18}
    [Size(status) = T3]
    OR {with probability=0.4}
    [Size(status) = T4]
    axiom 3 :IF Age(level)=[40-150]
    THEN {with probability=0.31}
    [Size(status) = T0-1]
    OR {with probability=0.46}
    [Size(status) = T2]
    OR {with probability=0.17}
    [Size(status) = T3]
    OR {with probability=0.6}
    [Size(status) = T4]
END RELATION (Size) depend from (Age)

Relation

*

RELATION (Grading) depend from (Positive axillary node)
    SOURCES      :Cancer 58:(2665)
    ARGUMENT1    :CONCEPT Grading
    ARGUMENT2    :CONCEPT Positive axillary node
    AXIOMS       :
    axiom 1      :IF Positive axillary node(status)=low
    THEN {with probability=0.26}
    [Grading(status) = 1]
    OR {with probability=0.46}
    [Grading(status) = 2]
    OR {with probability=0.28}
    [Grading(status) = 3]
    axiom 2      :IF Positive axillary node(status)=high
    THEN {with probability=0.18}
    [Grading(status) = 1]
    OR {with probability=0.52}
    [Grading(status) = 2]
    OR {with probability=0.30}
    [Grading(status) = 3]
END RELATION (Grading) depend from (Positive axillary
```

\*

```

RELATION (Positive axillary node) depend from (Age)
  SOURCES      :The Lancet 1990:335:(1566)
  ARGUMENT1    :CONCEPT Positive axillary node
  ARGUMENT2    :CONCEPT Age
  AXIOMS       :
    axiom 1 :IF Age(level)=[0-29]
              THEN {with probability=0}
                Positive axillary node(level) > 0
              OR {with probability=1}
                Positive axillary node(level) = 0
    axiom 2 :IF Age(level)=[30-39]
              THEN {with probability=0.12}
                Positive axillary node(level) > 0
              OR {with probability=0.87}
                Positive axillary node(level) = 0
    axiom 3 :IF Age(level)=[40-49]
              THEN {with probability=0.12}
                Positive axillary node(level) > 0
              OR {with probability=0.88}
                Positive axillary node(level) = 0
    axiom 4 :IF Age(level)=[50-59]
              THEN {with probability=0.7}
                Positive axillary node(level) > 0
              OR {with probability=0.93}
                Positive axillary node(level) = 0
    axiom 5 :IF Age(level)=[60-69]
              THEN {with probability=0.8}
                Positive axillary node(level) > 0
              OR {with probability=0.92}
                Positive axillary node(level) = 0
    axiom 6 :IF Age(level)=[70-150]
              THEN {with probability=0}
                Positive axillary node(level) > 0
              OR {with probability=1}
                Positive axillary node(level) = 0
  END RELATION (Positive axillary node) depend from (Age)

```

Relation

\*

```

RELATION (Size) depend from (Age)
  SOURCES      :The Lancet(1040)
  ARGUMENT1    :CONCEPT Size
  ARGUMENT2    :CONCEPT Age
  AXIOMS       :
    axiom 1    :IF Age(level)=[0-33]
                  THEN {with probability=0.26}

```

```

                                OR {with probability=0.56}
                                [ER(level) not determined
axiom 2 :IF Age(level)=[34-40]
                                THEN {with probability=0.30}
                                [ER(level) > 250 fmol/mg
                                OR {with probability=0.13}
                                [ER(level) < 250 fmol/mg
                                OR {with probability=0.57}
                                [ER(level) not determined
axiom 3 :IF Age(level)=[40-150]
                                THEN {with probability=0.31}
                                [ER(level) > 250 fmol/mg
                                OR {with probability=0.11}
                                [ER(level) < 250 fmol/mg
                                OR {with probability=0.58}
                                [ER(level) not determined
END RELATION (ER) depend from (Age)
```

Relation

\*

```

RELATION (PR) depend from (Age)
SOURCES      :The Lancet 1993:341:1040
ARGUMENT1    :CONCEPT PR
ARGUMENT2    :CONCEPT Age
AXIOMS       :
  axiom 1 :IF Age(level)=[0-33]
            THEN {with probability=0.41}
            [PR(level) > 250 fmol/mg
            OR {with probability=0.26}
            [PR(level) < 250 fmol/mg
            OR {with probability=0.33}
            [PR(level) not determined
  axiom 4 :IF Age(level)=[34-40]
            THEN {with probability=0.52}
            [PR(level) > 250 fmol/mg
            OR {with probability=0.20}
            [PR(level) < 250 fmol/mg
            OR {with probability=0.28}
            [PR(level) not determined
  axiom 7 :IF Age(level)=[40-150]
            THEN {with probability=0.51}
            [PR(level) > 250 fmol/mg
            OR {with probability=0.20}
            [PR(level) < 250 fmol/mg
            OR {with probability=0.29}
            [PR(level) not determined
END RELATION (PR) depend from (Age)
```

Relation

### Some relations in the domain model

Relation

go to prognostic factor

```
(Menopause) depend from (Age)
(ER) depend from (Age)
(PR) depend from (Age)
(Positive axillary node) depend from (Age)
(Size) depend from (Age)
(Grading) depend from (Positive axillary node)
(Grading) depend from (Menopause)
(Grading) depend from (Size)
(Grading) depend from (Peritumoral lymphatic vessel in-
vasion)
(Grading) depend from(ER)
(Age) depend from (Ploidy)
(Age) depend from (S-phase fraction)
(Nuclear grade) depend from (Ploidy)
(Nuclear grade) depend from (S-phase fraction)
(Size) depend from (Ploidy)
(Size) depend from (S-phase fraction)
(Positive axillary nodes) depend from (Ploidy)
(Positive axillary nodes) depend from (S-phase fraction)
(Positive axillary nodes) depend from (Size)
```

\*

```
RELATION (Menopause) depend from (Age)
  ARGUMENT1 :CONCEPT Menopause
  ARGUMENT2 :CONCEPT Age
  AXIOMS     :IF Age(level)=[0-50]
              THEN [menopause(status) = pre]
              IF Age(level)=[50-150]
              THEN [menopause(status) = post]
END RELATION (Menopause) depend from (Age)
```

Relation

\*

```
RELATION (ER) depend from (Age)
  SOURCES   :(The Lancet 1993:341:1040)
  ARGUMENT1 :CONCEPT ER
  ARGUMENT2 :CONCEPT Age
  AXIOMS    :
    axiom 1 :IF Age(level)=[0-33]
              THEN {with probability=0.28}
                [ER(level) > 250 fmol/mg]
              OR {with probability=0.16}
                [ER(level) < 250 fmol/mg]
```

```
      (T* and N3 and M0)  
      IV: (T* and N* and M1)  
END CONCEPT TNMstage
```

Concept

```

        status      :{normal,amplified}
END CONCEPT P53

```

Concept

\*

```

CONCEPT Her2/neu
  DESCRIPTION: oncogene whose level is measured by
              immunoperoxidase procedure
  SYNONYMS:  erbB-2; HER2/neu;
  SOURCES   :Cancer Research 52,1107-1113,1992
              Journal of Clinical Oncology 10(7):1044-
1048,1992
              Journal of Clinical Oncology 8(1):103-112,1990
  SUB TYPE OF:Oncogene expression
  PROPERTIES:
    status      :{positive ,negative}
    level       :{-,+,++}
  AXIOMS:
    positive:level = {++}
    negative:level = {-,+}
END CONCEPT Her2/neu

```

Concept

\*

```

CONCEPT TNMstage
  DESCRIPTION:clinical classification of brast cancer
(1992)
              -T:primary Tumor size
              -N:lymph Node status
              -M:distant metastasis
  SOURCES   :G.Bonadonna, Breast neoplasia(622)
  SUB TYPE OF:Size AND Axillary nodes AND metastasis
  PROPERTIES:
    stages     :{0,I,IIA;IIB,IIIA,IIIB,IV}
  AXIOMS:
    0:(Tis and N0 and M0)
    I:(T1 and N0 and M0)
    IIA:(T0 and N1 and M0) or
      (T1 and N1 and M0) or
      (T2 and N0 and M0)
    IIB:(T2 and N1 and M0) or
      (T3 and N0 and M0)
    IIIA:(T0 and N2 and M0) or
      (T1 and N2 and M0) or
      (T2 and N2 and M0) or
      (T3 and N1 and M0) or
      (T3 and N2 and M0)
    IIIB:(T4 and N* and M0) or

```

```
        status:{low,middle,high}
    AXIOMS:
        low   :(0-7)
        middle:(7-11.9)
        high  :(12-100)
    END CONCEPT S-phase fraction
```

Concept

\*

```
CONCEPT Ploidy
    DESCRIPTION:prolification indicator
    SOURCES      :Cancer 68:1465-1475,1991
    SUB TYPE OF:proliferative capacity
    PROPERTIES:
        status    :{diploid,aneuploid}
    END CONCEPT Ploidy
```

Concept

\*

```
CONCEPT Oncogene expression
    DESCRIPTION:whatever agent which is able to cause cancer;
it is generally used for proteins whose presence is related
to cancer.
    SUB TYPE OF:biologic
    END CONCEPT Oncogene expression
```

Concept

\*

```
CONCEPT C-myc
    DESCRIPTION:oncogene
    SOURCES      :Cancer Research 52,1107-1113,1992
    SUB TYPE OF:oncogene expression
    PROPERTIES:
        status    :{normal,amplified}
    END ONCEPT C-myc
```

Concept

\*

```
CONCEPT P53
    DESCRIPTION:protein oncogene
    SOURCES      :Journal of Clinical Oncology 12(3):454-
466,1994
    SUB TYPE OF:Oncogene expression
    PROPERTIES:
```

```

            8(6):1025-1035,1990
SUB TYPE OF:Hormonal receptor
PROPERTIES:
    unit      :{fmol/mg}
    level     :NUMBER-RANGE(0-infinite)
    status    :{positive,negative}

AXIOMS:
    positive:INTEGER-RANGE(0-9)
    negative:INTEGER-RANGE(10-infinite)
END CONCEPT PR

Concept

*

CONCEPT Proliferative capacity
    DESCRIPTION:proliferative activity gives information on
the reproduction speed of the tumoral cells.
    SOURCES      :The New England Journal of Medi-
cine(322):1045-1053
    SUB TYPE OF:Biologic
    PROPERTIES:
        status    :{low,high}
END CONCEPT Proliferative capacity

Concept

*

CONCEPT Thymidine labeling index
    DESCRIPTION: proliferative index given by the thymidine
index
    SUB TYPE OF:Proliferative capacity
    PROPERTIES:
        status    :{low,high}
END CONCEPT Thymidine labeling index

Concept

*

CONCEPT S-phase fraction
    DESCRIPTION: proliferative index given by
the fraction of cells in phase S.
(Flow cytometric measurements)
    SOURCES      :Cancer 68:1465-1475,1991
The New England Journal of Medicine(322)
:1045-1053
    SUB TYPE OF:Proliferative capacity
    PROPERTIES:
        unit:{%}

```



\*

```
CONCEPT Biologic
  DESCRIPTION: biologic prognostic factors
  SUB TYPE OF: Histologic
END CONCEPT Biologic
```

Concept

\*

```
CONCEPT Hormonal receptor
  DESCRIPTION: descriptors of hormonal substances
  TYPE OF: Biologic
END CONCEPT Hormonal receptor
```

Concept

\*

```
CONCEPT ER
  DESCRIPTION: estrogen are hormonal substances which favour the female growth, whose level is related to the mortality of breast cancer. A risk level (10 fmol/mg) has been so defined.
  SOURCES      :Breast Cancer Research and Treatment
                7(3):147-160,1986
                Journal of Clinical Oncology
                8(6):1025-1035,1990
  SUB TYPE OF: Hormonal receptor
  PROPERTIES:
    unit        : {fmol/mg}
    level       : NUMBER-RANGE(0-infinite)
    status      : {positive,negative}
  AXIOMS:
    positive: INTEGER-RANGE(0-9)
    negative: INTEGER-RANGE(10-infinite)
END CONCEPT ER
```

Concept

\*

```
CONCEPT PR
  DESCRIPTION: progesteron is an hormonal substance, whose level is related to the mortality of breast cancer. A risk level (10 fmol/mg) has been so defined.
  SOURCES      :Breast Cancer Research and Treatment
                7(3):147-160,1986
                journal of clinical oncology
```

```

DESCRIPTION:
    Nearly quantitative evaluation of the grade of malignant of the tumor based in terms of histologic parameters on a microscopic point of view. The following parameters are evaluated: tubular formation, nuclear polymorphism (irregularity in the dimension) and mitosi
    Specifically:
    Tubular formation:T
    1 score:well-defined
    2 score:medium
    3 score:low
    Polymorphism:P
    1 scorepunto:isomorph
    2 score:low in dimension, form and structure
    3 score:high
    Mitosi:M
    (peripheric exam in the sites of the tumor in which neoplastic tissue is present)
    1 score:occasional mitotic patterns
    2 score:two or three mitotic pattern observed
    3 score:high number of mitotic patterns
    SOURCES      :Cancer 65:2121-2128,1990;Cancer 58:2662-2670,1986
    SUB TYPE OF:Morphologic
    PROPERTIES:
    T level:INTEGER RANGE(1-3)
    P level:INTEGER RANGE(1-3)
    M level:INTEGER RANGE(1-3)
    level      :INTEGER RANGE(3-9)
    status     :{I,II,III}
    AXIOMS:
    level = T level+P level+M level
    I   :level=[3-5]
    II  :level=[6-7]
    III:level=[8-9]
END CONCEPT Grading

```

Concept

\*

```

CONCEPT Cellular
    DESCRIPTION:Semiquantitative evaluation of cytologic parameters
    SOURCES      :Cancer 65:2121-2128,1990;Cancer 58:2662-2670,1986
    SUB TYPE OF:Primary tumor prognostic factor
    PROPERTIES:
    status:{poor,good,unknown}
END CONCEPT Cellular

```

Concept

```
    SUB TYPE OF:Morphologic
    PROPERTIES:
        status:{positive,negative};
        region: NOMINAL;
END CONCEPT Necrosis
```

Concept

\*

```
CONCEPT Serial sectioning of ipsilateral axillary lymphnodes
    SOURCES      :Lancet(335);1565-1568,1990
    SUB TYPE OF:morphologic
    PROPERTIES:
        status:{positive,negative};
        lymph node: NOMINAL;
END CONCEPT Serial sectioning of ipsilateral axillary lymphnodes
```

Concept

\*

```
CONCEPT Tumor microvessels density
    SOURCES      :Journal of Clinical Oncology 12(3):454-466,1994
    SUB TYPE OF:morphologic
    PROPERTIES:
        status:{positive,negative};
END CONCEPT Tumor microvessels density
```

Concept

\*

```
CONCEPT Peritumoral lymphatic vessel invasion
    DESCRIPTION:nearly the 30% of breast cancers have an invasion of the peritumoral lymphatic vessels (external to the tumor) in the form of tumor embol. The tumor embol are groups of neoplastic cells come off from tumor mass.
    SOURCES      :G.Bonadonna, Breast neoplasia(622)
    SUB TYPE OF:morphologic
    PROPERTIES:
        status:{positive,negative}
END CONCEPT Peritumoral lymphatic vessel invasion
```

Concept

\*

```
CONCEPT Grading
```

Concept

\*

CONCEPT metastasis

DESCRIPTION: reproduction of the tumor at distance, due to the infiltration of cancer cells in the lymphatic or circulation system.

SOURCES :Lancet(335);1565-1568,1990

SUB TYPE OF:Anatomic stage

PROPERTIES:

status :{N0,N1,N2,N3,MX,M0,M1 }

AXIOMS :

N0 :no metastasis in regional lymph nodes

N1 :metastasis in mobile homolateral axillary lymph nodes

N2 :metastasis in fix homolateral axillary lymph nodes

N3 :metastasis in omolateral internal mammary lymph nodes

Mx :distant metastasis not checked

M0 :no distant metastasis

M1 :distant metastasis.

END CONCEPT metastasis

Concept

\*

CONCEPT Histologic

DESCRIPTION: histologic (that is regarding the tissue) prognostic factors

SUB TYPE OF:primary tumor prognostic factor

END CONCEPT Histologic

Concept

CONCEPT Morphologic

DESCRIPTION: morphologic (that is regarding the forme and the structure) prognostic factors

SUB TYPE OF:histologic

END CONCEPT Morphologic

Concept

\*

CONCEPT Necrosis

DESCRIPTION:necrosis is a complex of irreversible alterations of cellular, tissue, organ structure which implies their loss of living activity

SOURCES :journal of clinical oncology 11(10):1929-1935, 1993

```
CONCEPT Anatomic stage
  DESCRIPTION:Prognostic factors from an anatomic point of
  view. Anatomy studies the form and the structure of living
  being both from a microscopic and from a macroscopic point
  of view.
  SUB TYPE OF:Primary tumor prognostic factor
END CONCEPT Anatomic stage
```

Concept

\*

```
CONCEPT Positive axillary nodes
  DESCRIPTION:it is the most powerful prognostic factor;
  it describes the presence of lymphnodes in
  the axillary areas, which have been affected by the tumor,
  and as a consequence, in the dimension. In the case a lymph
  node is not affected, is classified as negative.
  SOURCES :Lancet 335(8705):1565-1568,1990
  SUB TYPE OF:Anatomic stage
  PROPERTIES:
    level :INTEGER-RANGE(0-infinite);
    status :{null,low,high}
  AXIOMS:
    null :NULL
    low :INTEGER-RANGE(1-3)
    high :INTEGER-RANGE(4-INFINITE)
END CONCEPT Positive axillary nodes
```

Concept

\*

```
CONCEPT Size
  DESCRIPTION:dimension of the primary tumor, expressed in
  cm.
  SUB TYPE OF:Anatomic stage
  PROPERTIES:
    unit :{cm}
    level :NUMBER-RANGE(0,infinite);
    status :{T0,T1,T1a,T1b,T1c,T2,T3,unknown}
  AXIOMS:
    T0 :NULL
    T1 :INTEGER-RANGE(0-2)
    T1a:INTEGER-RANGE(0-0.5)
    T1b:INTEGER-RANGE(0.5-1)
    T1c:INTEGER-RANGE(1-2)
    T2:INTEGER-RANGE(2-5)
    T3:INTEGER-RANGE(5-infinite)
    T4:whatever dimension, but with direct extension
  to the
    chest wall or to the skin.
END CONCEPT Size
```

## The primary tumor prognostic factor domain

Concept

go to Prognostic factor

go to relation

```

Primary tumor prognostic factor
  Anatomic stage
    Size
      TNMstage
    Positive axillary nodes
      TNMstage
    metastasis
      TNMstage
  Histologic
    Morphologic
      Grading
      Cellular
      Necrosis
      Serial sectioning of ipsilateral axillary lymphnodes
    Microvessels density
    Peritumoral lymphatic vessel invasion
  Biologic
    Hormonal receptor
      ER
      PR
    Proliferative capacity
      Thymidine labeling index
      S-phase fraction
      Ploidy
    Oncogene expression
      C-myc
      P53
      Her2/neu

```

\*

CONCEPT Primary tumor prognostic factor

DESCRIPTION:Prognostic factors related to the primary tumor. Primary tumor generally refers to the cancer tissue which has been surgically removed in the first surgical operation.

SUB TYPE OF:Breast cancer prognostic factor

END CONCEPT Primary tumor prognostic factor

Concept

\*

```
CONCEPT Brca-1
  DESCRIPTION:a gene whose mutation is related to the he-
    redity of breast cancer. A gene is a unit in a
    chromosome which controls heredity.
    (chromosome 17q21)
  SOURCES      :Science 266(5182):66-71,1994
  SUB TYPE OF:Tumor related prognostic factor
  PROPERTIES:
    status:{positive,negative}
  AXIOMS:
    positive : germ-line mutation=on
    negative : germ-line mutation=off
END CONCEPT Brca-1
```

Concept

\*

```
CONCEPT Brca-2
  DESCRIPTION:a gene whose mutation is related to the he-
    redity of breast cancer. A gene is a unit in a
    chromosome which controls heredity.
    (chromosome 13q12-13)
  SOURCES      :Science 266(5182):66-71,1994
  SUB TYPE OF:Tumor related prognostic factor
  PROPERTIES:
    status:{positive,negative};
  AXIOMS:
    positive : germ-line mutation=on
    negative : germ-line mutation=off
END CONCEPT Brca-2
```

Concept

END CONCEPT Hormonal therapy

Concept

\*

CONCEPT Other therapy

DESCRIPTION:

SOURCES :

SUB TYPE OF: Therapy prognostic factor

PROPERTIES:

status:{positive,negative};

END CONCEPT Other therapy

Concept

\*

CONCEPT Breast cancer prognostic factor

DESCRIPTION:Prognostic factors which refers to the disease in itself.

SUB TYPE OF:Prognostic factor

END CONCEPT Breast cancer prognostic factor

Concept

\*

CONCEPT Tumor-related prognostic factor

DESCRIPTION:Prognostic factors which are related to cancer itself but not to the cancer tissue.

SUB TYPE OF:Breast cancer prognostic factor

END CONCEPT Tumor related prognostic factor

Concept

\*

CONCEPT Recurrent tumor prognostic factor

DESCRIPTION:Prognostic factors which are related to the recurrent tumor; generally the recurrence of a secondary tumor (not metastasis) does not affect survival in prognosis.

SUB TYPE OF:Breast cancer prognostic factor

END CONCEPT Recurrent tumor prognostic factor

Concept

\*



```

SUB TYPE OF: Therapy prognostic factor
PROPERTIES:
  status:{positive,negative};
  cycle: {1, 2 ... n};
  drug: NOMINAL;
  quantity: REAL mg;
  frequency: {1,2 ... n weeks};
  date: DATE;
  elapsed time: {1,2 .... n days};
END CONCEPT  Chemotherapy
```

Concept

\*

```

CONCEPT  Radiotherapy
  DESCRIPTION: It is a therapy which focuses on the use of
               X-rays, in order to produce a biologic action
               on the human tissue, which can be selective since the tissue
               cells are characterised by a different radiosensitivity ac-
               cording to their activity and their development stadium.
  SOURCES      :G.Bonadonna, Breast neoplasia
  SUB TYPE OF: therapy prognostic factor
  PROPERTIES:
    status:{positive,negative};
    cycle: {1, 2 ... n};
    drug: NOMINAL;
    power: REAL Gy;
    frequency: {1,2 ... n weeks};
    target: NOMINAL;
    date: DATE;
    elapsed time: {1,2 .... n days};
END CONCEPT  Radiotherapy
```

Concept

\*

```

CONCEPT  Hormonal therapy
  DESCRIPTION: It is a therapy which focuses on the use of
               hormones; thias therapy was the only treatment
               before chemotherapy and radiotherapy were available.
  SOURCES      :G.Bonadonna, Breast neoplasia
  SUB TYPE OF: Therapy prognostic factor
  PROPERTIES:
    status:{positive,negative};
    cycle: {1, 2 ... n};
    drug: NOMINAL;
    dose: REAL;
    frequency: {1,2 ... n weeks};
    date: DATE;
    elapsed time: {1,2 .... n days};
```

```

    date: DATE;
END CONCEPT Blood transfusion

```

Concept

\*

```

CONCEPT Relative with breast cancer
  DESCRIPTION:relatives of the patient who are/were
               breast cancer affected
  SOURCES    :G.Bonadonna, Breast neoplasia:649-651
  PROPERTIES:
    level:INTEGER-RANGE(0-infinite)
  SUB TYPE OF:External factor
END CONCEPT Relative with breast cancer

```

Concept

\*

```

CONCEPT Therapy prognostic factor
  DESCRIPTION:the treatment which is given to the patient
               is obviously one of the most important
               prognostic factor
  SOURCES    :G.Bonadonna, Breast neoplasia
  SUB TYPE OF: Prognostic factor
END CONCEPT Therapy prognostic factor

```

Concept

\*

```

CONCEPT Surgical operation
  DESCRIPTION:Surgical operation already undergone
               by the patient
  SOURCES    :G.Bonadonna, Breast neoplasia
  PROPERTIES:
    status:{positive,negative};
    recurrnces:{0,1,... n};
    technique: {mastectomy, lampectomy, quadrantectomy}
  SUB TYPE OF: Therapy prognostic factor
END CONCEPT Surgical operation

```

Concept

\*

```

CONCEPT Chemotherapy
  DESCRIPTION: It is a therapy which focuses on the use of
               chemical drugs to treat diseases, specifically cancers.
               Chemotherapy is characterised by a chemotherapy index,
               which is obtained by the maximum toleration dose and the
               minimum curative dose ratio.
  SOURCES    :G.Bonadonna, Breast neoplasia

```

```

- more than 25 year-old.
- more than 30 year-old.
SOURCES :G.Bonadonna, Breast neoplasia:649-651
SUB TYPE OF:Physic characteristic
PROPERTIES:
    status:{Null,I,II};
END CONCEPT Pregnancy

Concept

*

CONCEPT Race
DESCRIPTION:race of the patient
SOURCES :Journal of the National Cancer Institute
        81(24):1879-1886,1989
SUB TYPE OF:Physic characteristic
PROPERTIES:
    status:{black,white,oriental};
END CONCEPT Race

Concept

*

CONCEPT stress
DESCRIPTION:process for which harmful stimula produce a
collection of reactive modifications of defence in the or-
ganism in order to annihilate them.This reponse is princi-
pally based on the action of the hormones produced in the
cortex part of the surkidney gland. If this action lasts
longtime, this may cause the «general syndrome of adapta-
tion».
SUB TYPE OF:External factor
PROPERTIES:
    status:{positive,negative};
END CONCEPT Stress

Concept

*

CONCEPT Blood transfusion
DESCRIPTION:therapeutic process which consists of
the introduction in the circulation system
of a certain amount of blood which has
been taken from another fellow.
SOURCES :Surgery 106(5):836-841,1989
SUB TYPE OF:External factor
PROPERTIES:
    status:{positive,negative};
```

```

        level:INTEGER-RANGE(0,150);
END CONCEPT Age

```

Concept

\*

```

CONCEPT Menopause
  DESCRIPTION:time when a woman ceases to menstruate, usu
              ally around the age (45,50)
  SOURCES    :G.Bonadonna, Breast neoplasia:649-651
  SUB TYPE OF:Physic characteristic
  PROPERTIES:
    status:{positive, negative};
END CONCEPT Menopause

```

Concept

\*

```

CONCEPT Overweight
  DESCRIPTION:the patients who weights too much
              may have a worst prognosis
  SOURCES    :Annals of Internal Medicine 120(1):18-25,1994
  SUB TYPE OF:Physic characteristic
  PROPERTIES:
    status:{positive,negative};
END CONCEPT Overweight

```

Concept

\*

```

CONCEPT General health
  DESCRIPTION:general health assessed by a specialistic
              visit
  SUB TYPE OF:Physic characteristic
  PROPERTIES:
    status:{good,bad};
END CONCEPT General health

```

Concept

\*

```

CONCEPT Pregnancy
  DESCRIPTION:pregnancy
              null:the patient has never had labour;
              first term pregnancy:
              two groups:

```

```
CONCEPT Prognostic factor
  DESCRIPTION:Factors which allow to predict
              the course of the disease
END CONCEPT Prognostic factor
```

Concept

\*

```
CONCEPT Patient prognostic factor
  DESCRIPTION:Prognostic factors dealing with the
              host (patient) characteristics
  SUB TYPE OF:Prognostic factor
END CONCEPT Patient prognostic factor
```

Concept

\*

```
CONCEPT External factor
  DESCRIPTION:Prognostic factors external to the host
  SUB TYPE OF:Patient prognostic factor
END CONCEPT External factor
```

Concept

\*

```
CONCEPT Physic characteristic
  DESCRIPTION:Prognostic factors dealing with the
              physic characteristics of the host. In general,
              as a latest results, these characteristics
              are not very related with prognosis, but
              may be very related to the risk factors to
              become ill.
  SUB TYPE OF:Patient prognostic factor
END CONCEPT Physic characteristic
```

Concept

\*

```
CONCEPT Age
  DESCRIPTION:the age of the patient is related to prog-
              nosis;specifically, prognosis in patients aged
              (0, 33) is usually worst; this is due to the
              greater frequency of positive axillary lymph
              nodes and high proliferative index cases.
  SOURCES      :Lancet 341(8852):1039-1043,1993
  SUB TYPE OF:Physic characteristic
  PROPERTIES:
```

## 7 Appendix B: the CommonKADS domain model for breast cancer prognosis

In this first part of our approach to the CommonKADS, we have obviously focused more on the domain knowledge. In this Appendix the last version of the domain knowledge is presented. In order to give a more structured version of the domain model, an HTML version is available in <http://www.inria.fr/acacia/personnel/rsacile/roberto.html>.

### The prognostic factor domain

\*

Concept

go to relation

prognostic factor

  Patient prognostic factor

    Physic characteristic

      Age

      Menopause

      General health

      Overweight

      Pregnancy

      Race

    External factor

      Stress

      Relative

      Blood transfusion

  Therapy prognostic factor

    Surgical operation

    Chemotherapy

    Radiotherapy

    Hormonal therapy

    Other therapy

  Breast cancer prognostic factor

    Tumor-related prognostic factor

      Brca-1

      Brca-2

    Primary tumor prognostic factor

    Recurrent tumor prognostic factor

\*

- biochemical test for liver function before starting adjuvant chemotherapy and after the third cycle.

At completion of adjuvant chemotherapy

- repeat biochemical tests if adjuvant chemotherapy is delivered for more than 3 cycles
- gynecological work-up with pelvic u.s. before starting tamoxifen.

Two months after completion of adjuvant chemotherapy + breast irradiation

- physical examination
- chest X-ray
- mammography (bilateral if conserving surgery)
- cardiac work-up (examination plus ECG)
- biochemical test if not performed at completion of adjuvant chemotherapy.

During the first five years from surgery (in the absence of suspicious findings)

- bone scan after 6 months from completion of adjuvant chemotherapy
- every 6 months
- physical examination
- CBC with differential and platelets
- biochemical tests
- chest X-ray
- every 12 months
- bone scan
- mammography (bilateral, if conserving surgery)
- ECG
- gynecologic examination plus pelvic ultrasounds (up to the first two years from completion of tamoxifen)

In all patients subjected to adjuvant CMF, Tamoxifen will be delivered at the dose of 20mg/day for 5 consecutive years, starting at the end of CMF.

In all patients subjected to conservative surgery followed by postoperative CMF, breast irradiation (max 60 Gy) will be delivered at the end of chemotherapy, either concomitantly or before tamoxifen.

#### ADJUVANT CHEMOTHERAPY IN OPERABLE BREAST CANCER IN WOMEN NOT SUBJECTED TO PRIMARY CHEMOTHERAPY

At surgery: FULL AXILLARY DISSECTION, TUMOR GRADE, CELL PROLIFERATIVE ACTIVITY, ESTROGEN RECEPTORS

Within 14 days after surgery

- if N- and POSITIVE ER and LOW PROLIFERATIVE ACTIVITY and DIFFERENTIATED TUMOR (variables measured at diagnosis and at major surgery)  
NO SYSTEMIC THERAPY  
BREAST IRRADIATION (max 60 Gy) AFTER CONSERVATIVE SURGERY
- if N- and NEGATIVE ER or HIGH PROLIFERATIVE ACTIVITY or UNDIFFERENTIATED TUMOR (variables measured at diagnosis and at major surgery)  
ADJUVANT CMF (C 600 mg/m<sup>2</sup> , M 40 mg/m<sup>2</sup> i, F 600 mg/m<sup>2</sup> , days 1 and 8, iv q. 4 weeks) for 3 or 6 cycles
- if N+ 1 to 3, regardless of other variables  
ADJUVANT CMF as above
- if N+ > 3, regardless of other variables  
ADJUVANT CMF (same dose and schedule) for 6 cycles.

#### FOLLOW-UP STUDIES

During adjuvant chemotherapy administration:

- complete blood counts with differential and platelets before each iv administration
- physical examination before starting any new cycle



FINE NEEDLE ASPIRATION (cell diagnosis, ER-ICA, PgR-ICA, Ki-67, nuclear grade)

Within 7 days from mammography:

- Day1Epirubicin 120 mg/m<sup>2</sup> iv
- Day22Epirubicin 120 mg/m<sup>2</sup> iv
- Day43Epirubicin 120 mg/m<sup>2</sup> iv
- Day63Repeat mammography, breast u.s., chest x-ray
- Day64SURGERY

- if at operating room  $T \leq 2.5 - 3$  cm, no scattered foci outside quadrant area:  
CONSERVATIVE SURGERY
- if at operating room  $AT > 3$  cm, or scattered foci outside quadrant area:  
MASTECTOMY

For both technical procedures: FULL AXILLARY DISSECTION, TUMOR GRADE, CELL PROLIFERATIVE ACTIVITY, ESTROGEN RECEPTORS

Within 14 days after surgery

- if N- and POSITIVE ER and LOW PROLIFERATIVE ACTIVITY and DIFFERENTIATED TUMOR (variables measured at diagnosis and at major surgery)  
NO SYSTEMIC THERAPY  
BREAST IRRADIATION (max 60 Gy) AFTER CONSERVATIVE SURGERY
- if N- and NEGATIVE ER or HIGH PROLIFERATIVE ACTIVITY or UNDIFFERENTIATED TUMOR (variables measured at diagnosis and at major surgery)  
ADJUVANT CMF (C 600 mg/m<sup>2</sup> , M 40 mg/m<sup>2</sup> i, F 600 mg/m<sup>2</sup> , days 1 and 8, iv q. 4 weeks) for 3 or 6 cycles
- if N+ 1 to 3, regardless of other variables  
ADJUVANT CMF as above
- if N+ > 3, regardless of other variables  
ADJUVANT CMF (same dose and schedule) for 6 cycles

If axillary nodes are histologically negative (or if surgery has not been performed) consider other variables determined either at diagnosis or at surgery:

- if **NEGATIVE ESTROGEN RECEPTOR** or **HIGH PROLIFERATIVE ACTIVITY** or **UNDIFFERENTIATED TUMOR** adjuvant chemotherapy should be delivered. A non-cross resistant adjuvant regimen is highly advisable (e.g. CMF days 1 and 8 q. 4 weeks for 3 or 6 cycles);
- if **POSITIVE ESTROGEN RECEPTOR** and **LOW PROLIFERATIVE ACTIVITY** and **DIFFERENTIATED TUMOR** no adjuvant systemic therapy should be delivered.

In patients subjected to adjuvant chemotherapy, tamoxifen can be delivered at the dose of 20 mg/day for 5 consecutive years, starting at the end of adjuvant chemotherapy.

In all patients subjected to conservative surgery, breast irradiation (max 60 Gy) will be delivered. When adjuvant chemotherapy is planned, breast irradiation should be started at the end of chemotherapy to avoid dose-intensity reductions.

## **PRIMARY CHEMOTHERAPY IN OPERABLE BREAST CANCER**

### **OPERATIONAL FLOW**

At palpation: T>2.5 cm, N0-2, M0

1) MAMMOGRAPHY

if T ≤ 2.5 cm --> conservative approach

if T > 2.5 cm

2) BREAST U.S.

TATTOO OF BREAST LESION

- PERFORM FINE NEEDLE ASPIRATION with sufficient material to allow determination of
  - cell diagnosis (malignant cells must be documented prior to start chemotherapy)
  - nuclear grade, estrogen and progesterone receptors with immunocytochemistry, cell proliferation activity (primary chemotherapy can achieve pathologic complete remission of the tumor and knowing about these variables can allow to assess whether patients need postoperative systemic treatment).

b. Within 7 days from diagnosis: start primary chemotherapy (e.g. epirubicin 120 mg/m<sup>2</sup> iv q.3 weeks for 3 cycles)

c. Within 3 weeks from the end of primary chemotherapy: repeat mammography and breast ultrasounds and compare imagins with those performed at diagnosis.

- if primary tumor measures <2.5 cm and no scattered foci at distance, consider conservative approach (e.g. quadrantectomy or lumpectomy with full axillary dissection)
- if primary tumor measures >3cm or scattered foci at distance are present, consider modified radical mastectomy with full axillary dissection

SURGERY (conservative or radical) must be performed within 3 weeks from the last dose of primary chemotherapy.

At surgery, if residual tumor is present in adequate quantity, tumor grade, cell proliferative activity and steroid receptors must be determined.

Within 14 days from surgery, postoperative systemic treatment, if needed, should be started.

In the presence of positive axillary nodes, postoperative chemotherapy should be delivered regardless of other prognostic variables and degree of primary tumor reduction. A non-cross resistant adjuvant regimen is highly advisable (e.g. CMF i.v. days 1 and 8 q. 4 weeks for 6 cycles).

## **6 Appendix A: skeleton of a guideline commonly used for breast cancer treatment in Italy**

The following documents are in relation to the operational procedures in two "protocols" for breast cancer treatment, one for primary chemotherapy and the second for adjuvant chemotherapy.

The following is copy as written by oncologists.

### **MULTIDISCIPLINARY TREATMENT IN OPERABLE BREAST CANCER**

a. At mammography:

- if, regardless of primary tumor diameters, scattered foci are present outside a quadrant; consider conventional surgical approach (e.g. modified radical mastectomy with full axillary dissection);

- if maximum tumor diameter is  $< 2.5$  cm and no scattered foci at distance: consider conservative approach (e.g. quadrantectomy or lumpectomy with full axillary dissection + breast irradiation);

- if maximum tumor diameter is  $> 2.5$  cm and no scattered foci at distance: consider primary chemotherapy to facilitate conservative approach and reduce the risk of local recurrence.

### **PRIMARY CHEMOTHERAPY IN OPERABLE BREAST CANCER**

a. Following mammography and breast ultrasound:

- TATTOO OF BREAST LESION (primary chemotherapy can reduce the size of the primary and thus will facilitate surgeons to consider initial shape of the primary)

- py. *Computers and biomedical research*, 19, 445-461.
12. Hadzikadic, M. (1992) Automated design of diagnostic systems. *Artificial Intelligence in Medicine*, 4, 5, 329-342.
  13. Renaud-Salis, J.L., Bonichon, F., Durand, M., Avril, A., Legarde, C., Serre, J.P. and Mendiboure, P. (1987) The SENEX system: a micro-computer-based expert system built by oncologists for breast cancer management. *Proceedings AIME87*, 54-70.
  14. Morio, S., Kawahara, S., Okamoto, N., Suzuki, T., Okamoto, T., Harada and M., Shimizu, A. (1989) An expert system for early detection of cancer of the breast. *Computers in Biology and Medicine*, 19, 5, 295-305.
  15. Blanchard, J.M., Chauvin, F., Clavel, M., Rubel, P. (1991) Therapeutic aid in oncology application of expert system for clinical research. *EXPERTSYS-91*, 387-392.
  16. Breuker, J. and Van de Velde W., editors (1994) *CommonKADS library for expertise modelling. Reusable problem solving components* (IOS Press, Amsterdam).
  17. Newell, A. (1982) The knowledge level. *Artificial Intelligence*, 18, 87-127.
  18. Schreiber, G., Wielinga, B., Akkermans, H., Van de Velde, W. and Anjewierden, A. (1994) CML: the CommonKADS Conceptual Modelling Language. *Proceedings EKAW'94, LNAI 867*, 1-25 (Springer-Verlag, Heidelberg, FRG).
  19. Linster, M. and Musen, M.A. (1992) Use of KADS to create a conceptual model of the ONCOCIN task. *Knowledge Acquisition*, 4, 55-87.
  20. Schreiber, A.Th., Terpstra, P., Magni, P. and van Velzen M. (1994) Analysing and implementing VT using COMMON-KADS. *Proceedings of the 8th Banff Knowledge Acquisition for Knowledge Based Systems Workshop*, 3, 44-1 - 44-29.
  21. Bredeweg, B. (1993) Qualitative prediction of behaviour. In Bredeweg B. Schreiber, G., Wielinga, B. and Breuker, J., editors, *KADS: a principled approach to knowledge-based system development* (Academic Press, London).
  22. Forbus, K.D. (1984) Qualitative process theory. *Artificial Intelligence*, 24, 85-168.
  23. Gaglio, S., Genovesi, M., Ruggiero, C., Spinelli, G., Nicolini, C., Bonadonna, G. and Valagussa, P. (1987) Expert systems for cancer chemotherapy. *Comput.Math.Applic.*, 14, 9-12, 793-802.
  24. Gaglio, S., Giacomini, M., Nicolini, C., and Ruggiero, C. (1991) A qualitative approach to cell growth modeling and simulation for cancer chemotherapy. *IEEE Transactions on Biomedical Engineering*, 38, 4, 386-389.

## 5 References

### 5.1 References used in this technical report

1. Fisher, B., Bauer, M., Wickerham, D.L., Redmond, C.K. and Fisher E.R. (1983) Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. *Cancer*, 52, 1551-1557.
2. Bonadonna, G. and Valagussa P. (1989) Systemic therapy in resectable breast cancer. *Hematol. Oncol. Clin. North Amer.*, 3, 727-742.
3. Pritchard, K.I. (1989) Systemic adjuvant therapy for node-negative breast cancer: proven or premature. *Ann. Int. Med.*, 111, 1-4.
4. Osborne, C.K. (1990) Prognostic factors in breast cancer. In: De Vita V.T. Jr., Hellman S. and Rosenberg S.A. *Cancer. Principles and practise of oncology*, 1-11 (Lippincott, Philadelphia).
5. Fisher, B., Redmond, C. and Fisher, E.R. (1988) Relative worth of estrogen or progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: findings from Nutritional Surgical Adjuvant Breast and Bowel Project Protocol B-06. *Journal of Clinical Oncology*, 6, 1076-1087.
6. Bacus, S.S., Zelnick, C.R., Plowman, G. and Yarden Y. (1994) Expression of the erbB-2 family of growth and their ligands in breast cancer. *American Journal of Clinical Pathology*, 102, 4, suppl.1, 13-23.
7. Upadhyay, J.L., Ghosh, B.N. and Sengupta, I.N. (1991) International channel of communication for breast cancer literature. *International Information, Communication and Education*, 10, 1, 48-59.
8. Norman, D.A., (1988) *The psychology of everyday things* (Basic Books, New York).
9. Shortliffe, E., Scott, A., Bischoff, M., van Melleand, C. and Jacobs W. (1981) ONCOCIN: An expert system for oncology protocol management. *Proceedings IJCAI81*, 876-881.
10. Tu, S.W., Kahn, M.G., Musen, M.A., Ferguson, J.C., Shortliffe, E.H. and Fagan, L.M. (1989) Episodic skeletal-plan refinement based on temporal data. *Communication of the ACM*, 32, 12, 1439-1455.
11. Gaglio, S., Ruggiero, C., Spinelli, G., Bonadonna, G., Valagussa, P. and Nicolini, C. (1986) BREASTCAN: an expert system for postoperative breast cancer thera-

ified, as well its reliability (in this case also the term “axiom” should be revised); the introduction of some kind of function should be allowed to avoid long lists of similar axioms, like in TNM\_stage. The task knowledge does not provide any representation to decompose tasks in sub-tasks which are not sequential; such as, for example, in the prognostic task, it is not easy to represent the assessment deriving from literature consultation, even if this updating is intrinsic to a possible model of a human expert in oncology.

In conclusion, although the work presented here may be interpreted just as an exercise of CommonKADS application in the medical domain, the conceptual model we have obtained seems to reflect well the new trends of breast cancer prognosis; besides, we are still far from a design model of the prognostic system, and from verifying the gap between conceptual and design model which has been addressed in [19] as one of the worse features of KADS-I methodology. From this experience, we can conclude that CommonKADS has been a good support for conceptualisation, although its standardisation process has not finished yet, and a standard, leading tool is needed to support it.

The guideline (GL) database is the real core of the system; specifically its formalism as well as its level of abstraction has to be defined in order to comply a trade-off between natural language and computer language structure. The need of a representation which is not distant from the natural language is due to the very fact that a guideline should always have a correspondent in natural language (a sort of guideline “book”). Besides, it is feasible that in the next few years multimedia and/or networking techniques will be used to describe guidelines; in this case, although guidelines are still expressed in natural language, a greater effort in structuring the GL contents will be performed. Finally, guidelines might become object of the inferring of knowledge based systems (KBS) as well as of other applications, so in this case GLs should be expressed in a language which is highly structured in order to infer on it and to allow a fast access to a specific content; moreover a highly structured language will be necessary to automatate the guideline building process. CML may be a good candidate for this representation.

## 4.2 Conclusions

Our conclusion is that CommonKADS was a satisfactory methodology to conceptualise prognosis, since it guided us to approach the problem in a structured way; first, we decomposed the prognostic task into subtasks which were already defined in the CommonKADS library; subsequently, we defined the domain knowledge involved, following CML; then we defined the inference layer following the library, and finally we defined the task knowledge. Following this conceptualisation, we have found a significant help; specifically, exploding the prognostic process has allowed us to find a problem definition which fits well the needs of a modern definition of prognosis, and which can reuse the models already developed in the library; the domain knowledge and its CML definition allows a good definition of a glossary of the terminology used and it is also a good way to approach knowledge acquisition both from literature and from human experts; in the latter case, CML has been found an easy language to have a dialogue with experts, who could directly evaluate the evolution of the work. The inference knowledge and the task knowledge have given us a trace of models that can be reusable for our aim.

On the other hand, CommonKADS is not a cookbook for building expert systems [19], yet. The research in the CommonKADS library of generic models is not easy, since some models have not been developed to a great extent (i.e. the qualitative model); in some cases (i.e. prediction model) the reader has to refer to the work done in previous releases (KADS-I) thus facing in changes of terms and approaches. Besides, the CML is commonly used in a grammar that is more practical in some aspects than the one we have referred to; in our opinion, further work is needed also in CML; for example, concept and relation axioms are a central issue in modelling a domain when starting from a knowledge acquisition process and their role should be stressed and deeply formalised; for example, the source of an axiom should be spec-



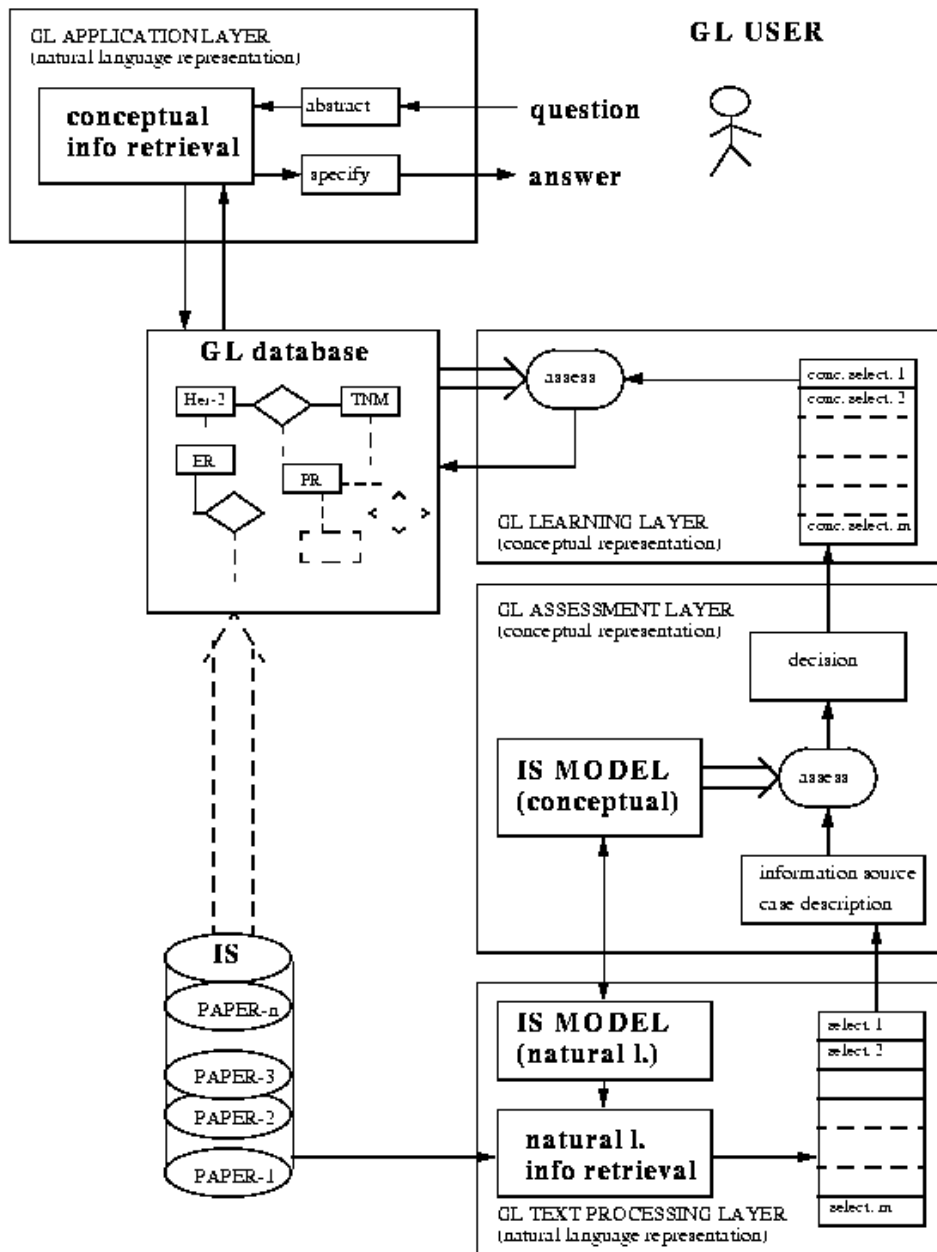


Figure 11 : A guideline system architecture.

In this respect, the results of the knowledge acquisition process may be viewed as a guidelines (GL) database which can be used to produce guidelines as well as to be accessed by computers applications (see fig.10).

With respect to GL productions, a system which guides the conceptualisation of the knowledge contained in a paper should represent a valid help in the production of a guideline. In a future development of this work, the definition of a conceptual information retrieval system for the production of guidelines on prognostic factors of breast cancer should be also addressed.

There are several medical models that have been implemented which address different aspects of this domain, such as, for example, ICD9 (International Classification of Diseases with Clinical Modifications), GMN (Gabrieli Medical Nomenclature) and GALEN (Generalized Architecture for Languages, Encyclopaedias and Nomenclatures in Medicine).

A possible architecture of the global system we propose is shown in fig.11. We propose a four-layered architecture. The text processing layer processes the information source (IS) database in order to select the papers which contain the topics addressed by the guideline. This can be performed by a traditional information retrieval (IR) system which can select from IS the papers which address a specific topic (modelled in an IS model, in the form of boolean expressions of keywords). The service given to the upper layer is a queue of papers which satisfy the information needs of the addressed GL modelled in the IS model.

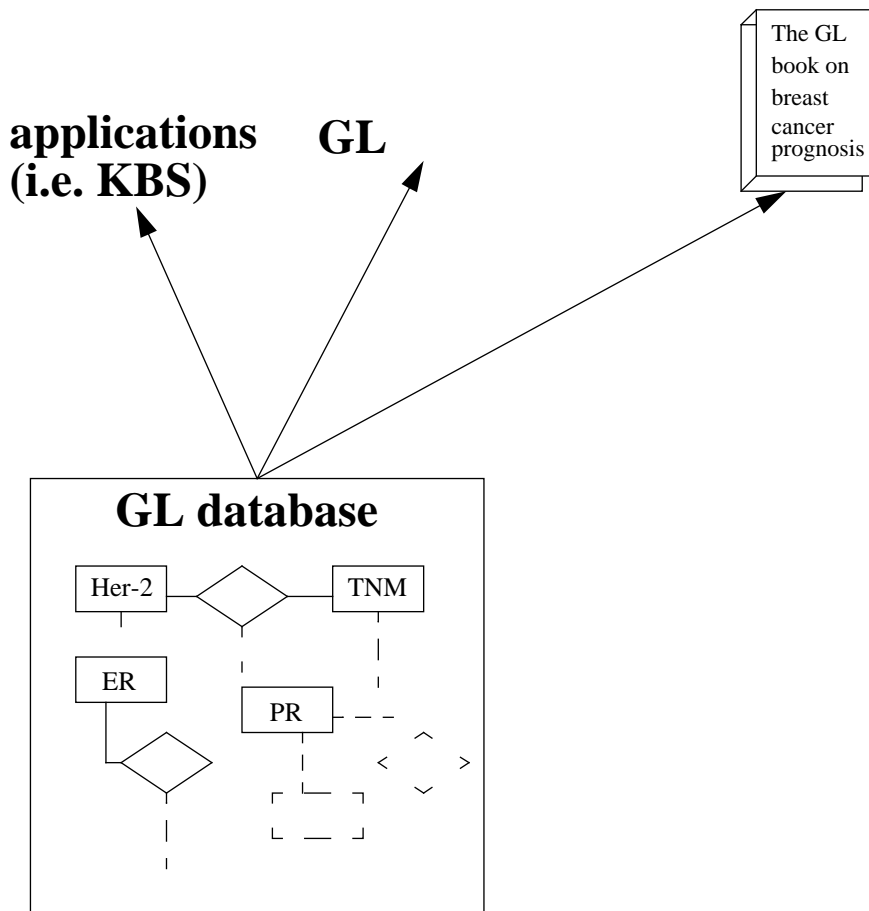
The assessment layer performs the conceptualisation of the papers selected at the text processing layer. Each selected paper is abstracted and compared with an IS conceptual model, which defines the syntax, the relations and the constraints of the concepts which should be contained in the current selected paper in an abstract formalism. The services provided to the upper layer is the result of this comparison, which is assessed in a decision which contains the abstracted structure of the selected paper as well as parameters indicating its compliance with quality criteria.

The learning layer stores the decisions given from the assessment layer. The service of this layer is to update the guideline. An assessment task compares the GL database with each element of the queue; the result of the assessment may be either an updating of the GL database with the results presented in the paper or a decision of not taking into account those results.

## 4 Future developments and conclusions

### 4.1 A conceptual information retrieval system for the production of guidelines on prognostic factors of breast cancer

The first steps of a guideline production are the reading of the literature on a specific topic, the conceptualisation and the understanding of it, and the assessment whether the concepts contained in it are proper to be added or to modify the guidelines which concern this topic (such as, for example, according to criteria about the quality of the research). The key point of this process is the knowledge conceptualisation and the result understanding.



**Figure 10 :** A guideline database containing the conceptual structure of the breast cancer prognosis (and therapy) domain should have different applications, such as, for ex. the production of guidelines, the consultation by KBS, the management of guidelines for updating...

### 3.4 A simplified model for breast cancer treatment in CML

One of the main problems of actual release of CommonKADS methodology is that it lacks of a standard, leading tool which can guide the user in the application of the whole methodology. Other methodology, such as Protege from Stanford University, do not have this problem since the methodology has followed the evolution of a related software tool.

For CommonKADS, the KADS\_tool is one of the best known tools to use CommonKADS, but it presents many features from KADS-I which has been overcome in CommonKADS.

It is the author's opinion that a CommonKADS-dedicated tool should be strictly adherent to the CommonKADS standard and, first of all, to CML, the conceptual modelling language which has been recommended to CommonKADS.

The KACTUS toolkit, by the University of Amsterdam and Cap Programator (Stockholm), supports CML. KACTUS is an interactive environment for browsing, editing and managing (libraries of) ontologies. The toolkit is currently under development. One of the aims of KACTUS is to support reuse of ontologies, in other to support this, the toolkit can handle various ontology formalisms (CML, EXPRESS and Ontolingua) and can perform (partial) translations between these formalisms.

Specifically, in the group ACACIA, a CML-supporting tool, COKACE (CommonKADS Centaur) is under development. This tool has been developed with the CENTAUR environment, also developed at INRIA. COKACE, allows to develop a CML model according to the CML standard definition, to check its consistency and to interpret it. Since a first version of the tool has been available in these last few days, and anyway it is always better to test tools on easier examples, a simplified example of the breast cancer prognostic problem has been developed. In this example, some factors have been regarded as a biological manifestation; this biological manifestation can produce risk factors. The combination of risk factors produced as well as risk factors given as user input, can produce a risk as a result, which may assume the high value and the low value. In section 8 page 72 (Appendix C), this model has been reported.

Obviously, the advantage of using a tool is that it constrains the knowledge engineer to a more realistic version of its conceptual model. Besides, the risk of a tool very related to a language is to become nothing but a shell for software production. It is the author's opinion, that to overcome this risk, the next step to be performed in the COKACE tool, is to give the user a collection of reusable models (specifically, inference and task knowledge) to be «cut & pasted» in the user application.

**TASK** bc\_prognosis

**TASK-DEFINITION**

**GOAL:** to predict the evolution of breast cancer (bc) disease at least in terms of survival and disease-free time

**INPUT:**

prognostic factors: the set of prognostic factors about bc in a patient model description: set of parameter/value pairs to define a partial bc description

therapy: previous, actual and proposed therapy for that bc

**OUTPUT:**

evolution of the disease: survival time, disease free, recurrences ....

messages: needs of other prognostic factors, needs of controlling improbable values...

**TASK-BODY**

**TYPE:** composite

**sub-tasks:** bc\_assess, bc\_update, bc\_predict

**ADDITIONAL-ROLES:**

decision: a set of data, referring to the input prognostic factor, for ex., the value of the prognostic factor, if the procedures to determine it were fitted to guidelines, whether considering or not this prognostic factor...

model of prognostic factors: abstracted guideline on prognostic factors

model description: description of bc on which evolution should be predicted

**CONTROL-STRUCTURE:**

bc\_prognosis ( prognostic factors + model description + therapy → evolution + messages) =

REPEAT

; assess the value and reliability of a specified prognostic factor

bc\_assess (prognostic factor + model of prognostic factors → decision);

UNTIL there are any input specification for prognostic factors

; update the model description, both from input description and from decisions

bc\_update (model description + decision → model description)

; predict the evolution of bc, thus predicting also evolution and giving control messages

bc\_predict (model description → model description + evolution + messages);

**END TASK** bc\_prognosis

**Figure 9 :** The task knowledge of the prognostic system.

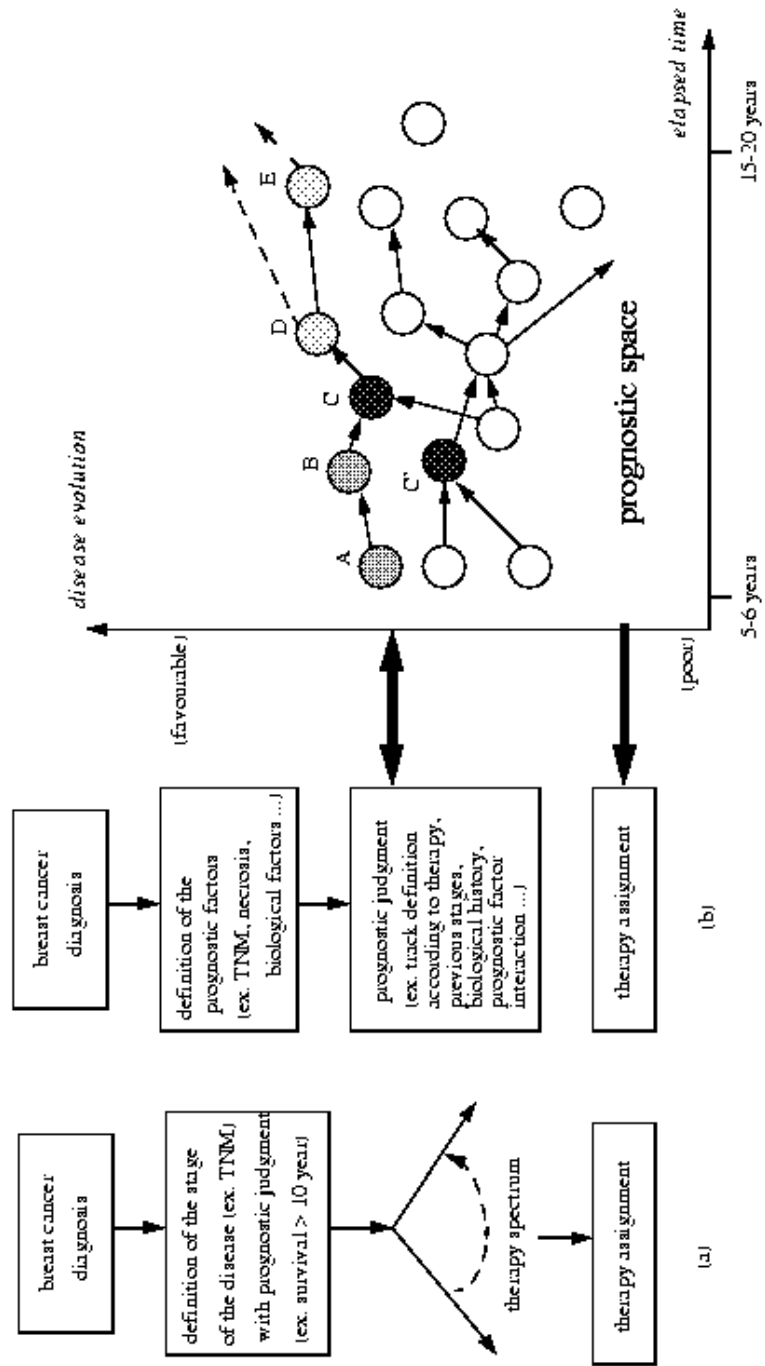


FIGURE 8

Starting from this, past states (A, B) and future states (D, E) should be predicted, thus defining the track (A, B, C, D, E). The choice of the proper therapy will come from this track definition.

In this case, the addition of information from literature to the system should not need a reinterpretation of the qualitative model or of the assessment model, but an upgrade of the primitive inferences.

### **3.3.5. The task knowledge**

Oncology is perhaps one of the more knowledge structured domain of medicine, in which task as diagnosis, assessment, scheduling are continuously studied and applied.

Specifically, the primitive task knowledge involved in prognosis are assessment and prediction (as defined by fig2d); fig.9 shows the root task knowledge of the prognostic task, which can be decomposed in an assessment, a prediction and an updating task. As refers to assessment and prediction task, their refinement reflects the correspondent CommonKADS library of generic models, while the updating task is just a combination of “specify” inferences on the system model.

Besides, when dealing with task knowledge, we should focus on two separate modules: an assessment task for the updating of the prognostic system from literature and the prognostic system itself composed by assessment and prediction. The connection between these two modules is not really straightforward; in the sense that updating may depend on prognosis, but it can also “run” independently, that is when some “stimulus” is present. Some techniques currently not provided by CommonKADS should be needed to solve the problem; fig.9 does not take into account the updating from literature.

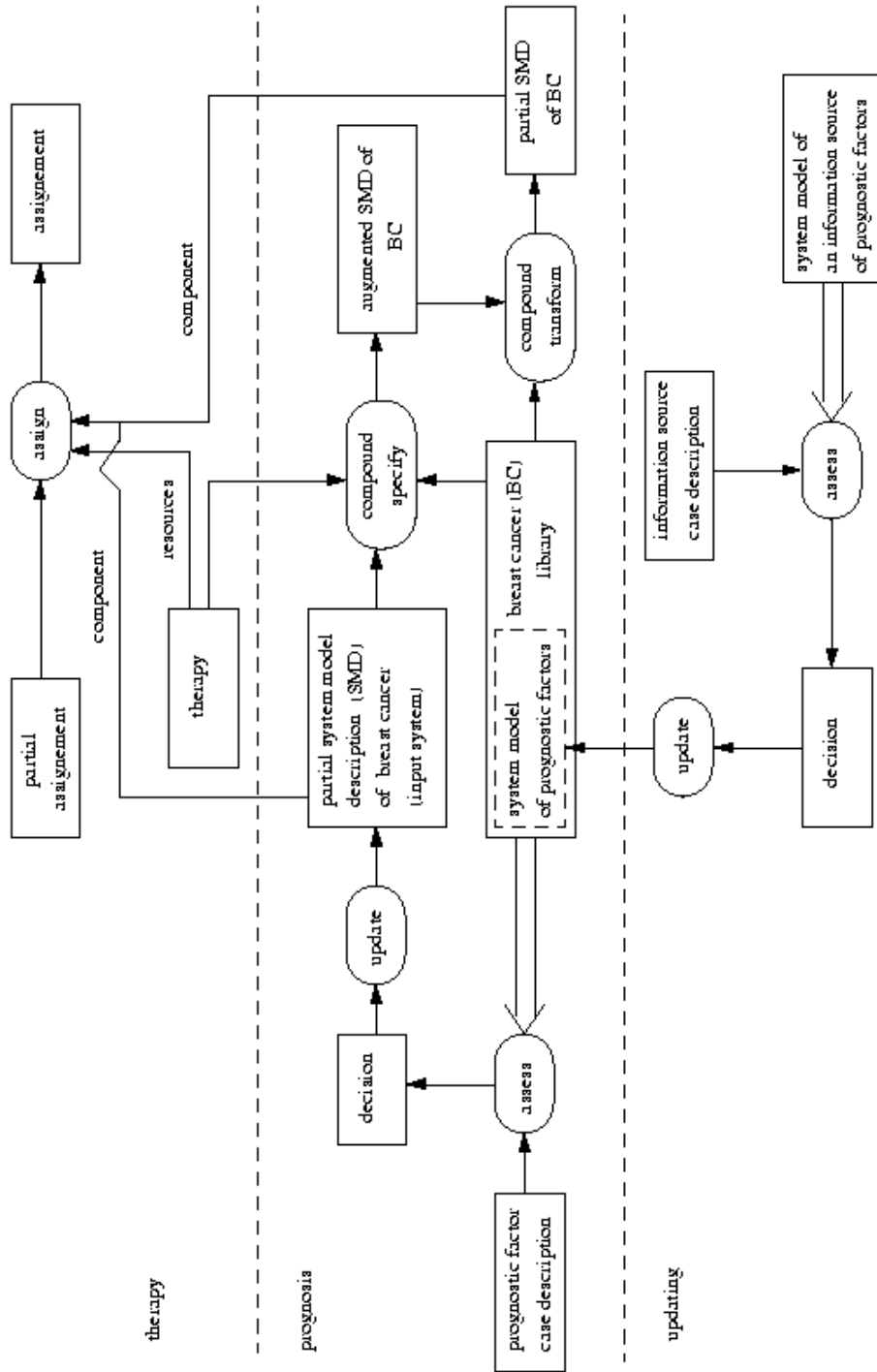


FIGURE 7



In theory, the addition to the system of information from literature should not need a reinterpretation of the domain, if a good work of abstraction has been done in considering all the possible classes of prognostic factors and the possible influences on the behaviour of the tasks. As an easy example, if the HER2 prognostic factor were not included in the model, its super-concept “oncogene” must be present, thus allowing a new instantiation of it, as well as of the referring axioms. In the case a prognostic factor is already present, but a different (or in agreement) interpretation is given from literature, the system should “properly” update the axioms and the relations involved. In section 7 page 43 (Appendix B), the skeleton of the domain knowledge of breast cancer prognosis is shown. This information can be easily read by consulting <http://www.inria.fr/acacia/personnel/rsacile/roberto.html>.

#### **3.3.4. The inference knowledge**

The inference structure (fig.7) reflects the prediction inference knowledge by [21], the assessment inference knowledge by [16, chap.7]; and the preliminary definition of the assignment inference knowledge by [16, chap.11]. Besides, following the CommonKADS library of generic models, we should have a guide to describe our conceptual model in more detail.

Prognosis is in the middle layer of fig.7, that is an assessment task on prognostic factors of the patient and a prediction task of breast cancer behaviour; the assessment on prognostic factors extracted from literature is in the lower layer, while therapy is in the upper layer. The system model of prognostic factor is a static role when referred by prognosis, but it can be updated by the assessment on information source. The prediction is strongly related to the development of a qualitative model of breast cancer, since the relations and the parameters in this domain are “naturally” qualitative rather than quantitative; this model is currently being in phase of development, following [21, 22] and some specific previous work [23, 24]. The transition between one state and another of the qualitative model is determined both by the biological features of the tumour and by the values of prognostic factors, including therapy. The qualitative model should predict the future state (and the therapy will be the variable that should optimise prognosis) as well as the past states (identified also by other previous information, such as for example, the clinical card of the patient). The identification of the past states will be used for a better identification of the track corresponding to the tumour evolution (fig.8), and, as a consequence, to an improved definition of the current stage. A qualitative model of breast cancer should cover the prognostic space with states and transitions. Nowadays, prognosis is not only the result of an assessed stage of the disease, but it may be regarded as the research in the prognostic space (defined as “disease evolution x elapsed times” from the cancer birth) of the evolution track related to the current patient. As a first step, prognosis should consist of assessing breast cancer stage and prognostic factors; this should define probable milestones of the track (fig.8b, C, C’).

**CONCEPT** *TNM\_stage*

**DESCRIPTION:** "This staging system provides a strategy for grouping patients with respect to prognosis. Therapeutic decisions are formulated in part according to staging categories but primarily according to lymph node status, ER and PR receptor levels in the tumour tissue, menopausal status, and the general health of the patient. TNM stages are defined by primary tumour (T), regional lymph nodes (N) and pathologic classification (pN), distant metastasis (M)."

**SOURCES:** 1. Breast. In: American Joint Committee on Cancer: Manual for Staging of Cancer. Philadelphia: JB Lippincott Company, 4th ed., 1992, pp 149-154.

**SUB-TYPE-OF:** size, axillary nodes, metastasis

**PROPERTIES:**

```

stage
  VALUE-SET stages;
  TYPE: NOMINAL;
  VALUE-LIST:=, I, IIA, IIB, IIIA, IIIB, IV;
  VALUE-SPEC:text;
  END VALUE-SET stages

```

**AXIOMS:**

$\forall T:\text{size } N:\text{axillary\_node } M:\text{metastasis } \text{TNM}:\text{TNM\_stage}$

```

has_status(T, Tis)  $\wedge$  has_status(N, N0)  $\wedge$  has_status(M, M0)
 $\rightarrow$  has_status (TNM, 0);
has_status(T, T1)  $\wedge$  has_status(N, N0)  $\wedge$  has_status(M, M0)
 $\rightarrow$  has_status(TNM, I);
(has_status(T, T0)  $\wedge$  has_status(N, N1)  $\wedge$  has_status(M, M0))  $\vee$ 
(has_status(T, T1)  $\wedge$  has_status(N, N1)  $\wedge$  has_status(M, M0))  $\vee$ 
(has_status(T, T2)  $\wedge$  has_status(N, N0)  $\wedge$  has_status(M, M0))
 $\rightarrow$  has_status(TNM, IIA);
(has_status(T, T2)  $\wedge$  has_status(N, N1)  $\wedge$  has_status(M, M0))  $\vee$ 
(has_status(T, T3)  $\wedge$  has_status(N, N0)  $\wedge$  has_status(M, M0))
 $\rightarrow$  has_status(TNM, IIB);
(has_status(T, T0)  $\wedge$  has_status (N, N2)  $\wedge$  has_status (M, M0))  $\vee$ 
(has_status(T, T1)  $\wedge$  has_status (N, N2)  $\wedge$  has_status (M, M0))  $\vee$ 
(has_status(T, T2)  $\wedge$  has_status (N, N2)  $\wedge$  has_status (M, M0))  $\vee$ 
(has_status(T, T3)  $\wedge$  has_status (N, N1)  $\wedge$  has_status (M, M0))  $\vee$ 
(has_status(T, T3)  $\wedge$  has_status (N, N2)  $\wedge$  has_status (M, M0))
 $\rightarrow$  has_status (TNM, IIIA);
(has_status (T, T4)  $\wedge$  has_status (M, M0))  $\vee$ 
(has_status (N, N3)  $\wedge$  has_status (M, M0))
 $\rightarrow$  has_status (TNM, IIIB);
has_status (M, M1)
 $\rightarrow$  has_status (TNM, IV);

```

**END CONCEPT** *TNM\_stage*

FIGURE 6

**CONCEPT HER2**

**DESCRIPTION:** "a proto-oncogene whose overexpression is likely to have a direct impact on cellular growth control and to the aggressiveness of the tumour."

**SYNONYMS:** erbB-2; HER2/neu

**SOURCES:** 1. Bacus S., Zelnick C., Plowman G. and Yarden Y. "Expression of the erbB-2 family of growth factor receptors and their ligands in breast cancer".....

**SUB-TYPE-OF:** proto-oncogene

**PROPERTIES:**

```
overexpression
  VALUE-SET qualitative_value;
  TYPE: NOMINAL;
  VALUE-LIST: +, -
  VALUE-SPEC:text;
END VALUE-SET overexpression
```

...

**END CONCEPT HER-2**

**CONCEPT Immunoperoxidase**

**DESCRIPTION:** "Paraffin sections are cut from tissue blocks on poly-L-lysine coated slides. After the sections are de-waxed and rehydrated, they are treated with 0.1% protease for 20 minutes at 20°C to 22°C. This is followed by incubation with a mouse monoclonal antibody (4 mg/mL overnight at 4°C) to the external domain of the HER-2 protein. Bound antibodies are demonstrated by the avin-biotin-peroxidase sequence. The sections are counterstained with methyl green."

**SOURCES:** 1. Toikkanen S. et al.. "Prognostic significance of HER-2 oncoprotein expression in breast cancer: a 30-year follow-up".....

**SUB-TYPE-OF:** prognostic laboratory test

**PROPERTIES:**

```
stain_intensity
  VALUE-SET qualitative_value;
  TYPE: NOMINAL;
  VALUE-LIST: -, +, ++
  VALUE-SPEC:text;
END VALUE-SET stain_intensity
```

...

**END CONCEPT Immunoperoxidase**

**FIGURE 6** (following in the next page)

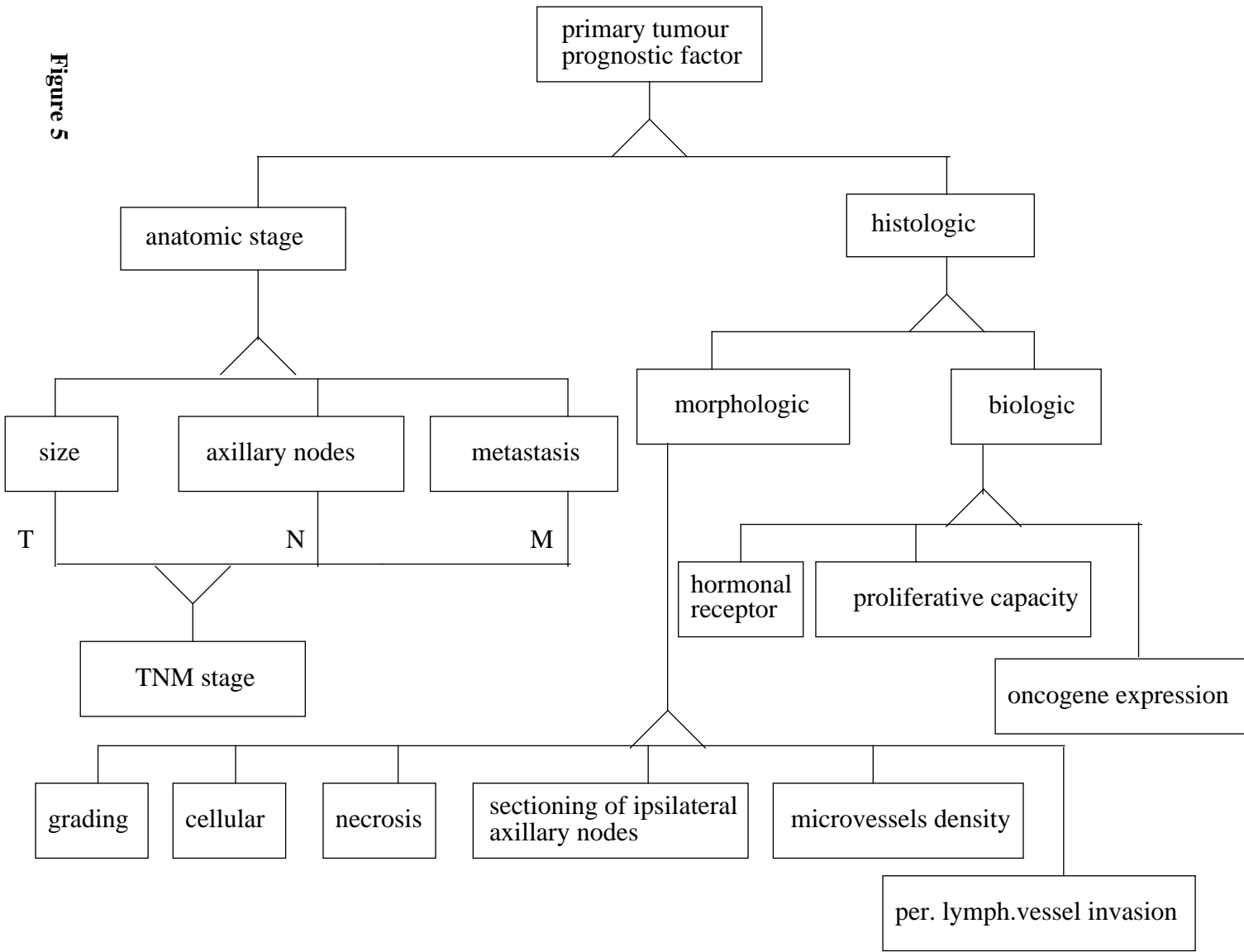


Figure 5

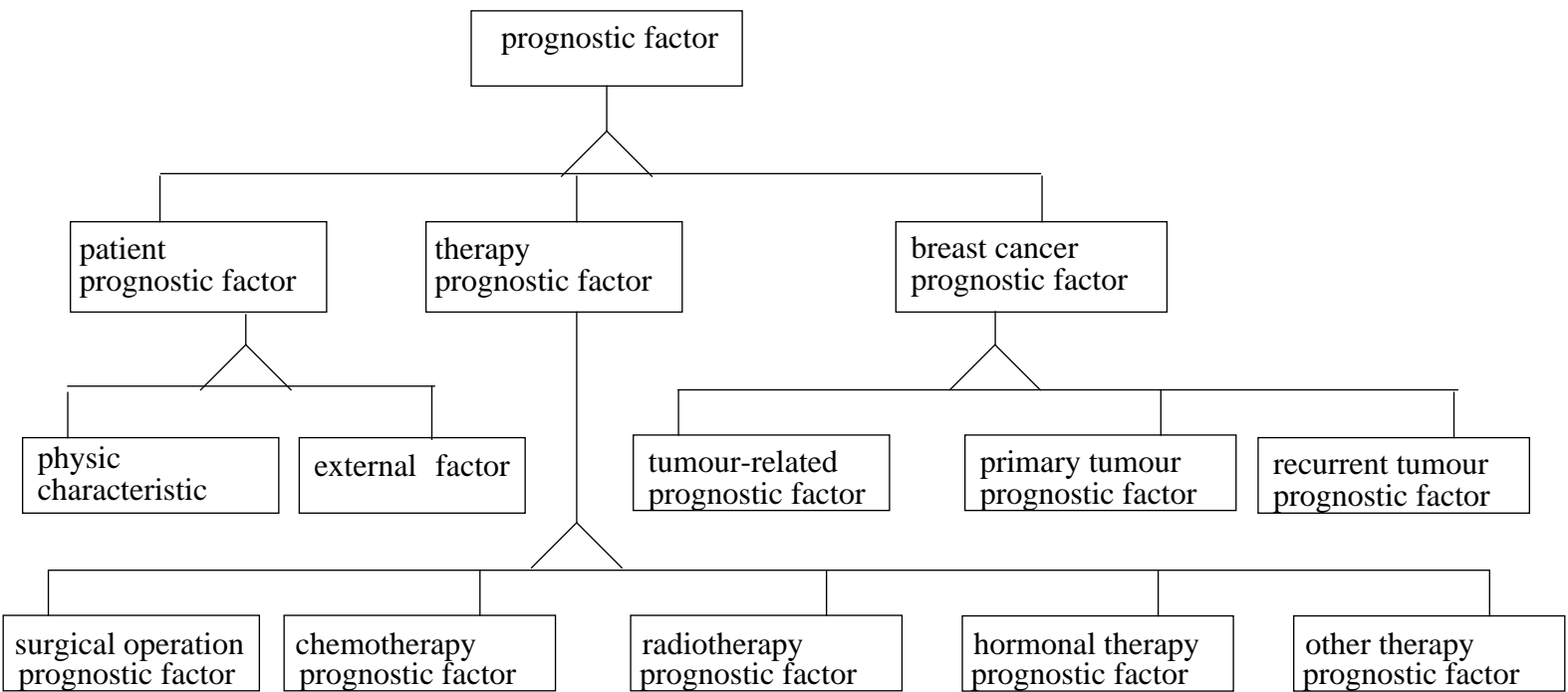


Figure 4

port, etc.; so, it should also be assessed whether it is worthwhile to add the knowledge deriving from this article to the assessment and prediction system models in order to improve the prognostic judgement and, as a consequence, a proper therapy. This assessment task does not take part of the chain of the expert tasks for patient management; it is in a certain way an optional task (a task in which the whole system is updated), or a task which is performed “now and again”, that is at sample periods or when a case needs a better evaluation.

In conclusion, we regard patient management as the collection of tasks of fig.2d (like in [16, chap.4], this chain, as well as the previous ones, reflects dependencies not an order of processing). This collection corresponds to 1) diagnosis, 2) prognosis 3) selection of therapy, 4) follow-up. The aim of our conceptualisation is 2).

After having defined the generic models which should be suited to our problem, we can conceptualise it; the CommonKADS conceptualisation of the breast cancer prognosis should be in terms, at least, of a description of the domain, inference and task knowledge involved in the problem.

### 3.3.3. The domain knowledge

Within the domain knowledge, we construct the axiomatic structure; this takes the form of producing a domain lexicon and a concept hierarchy. With respect to this and to our data sources, we have defined a hierarchy of ontologies [18]; fig.3 shows the root schema of the domain level; fig.4 shows the domain knowledge of the prognostic problem. As regards concepts, we have defined seven “primitive” concepts, that are: patient, breast cancer, information source, prognostic factor, prognosis, therapy and laboratory test (general, prognostic and therapy). Fig. 5 and 6 show the “is-a” concept hierarchy for the “prognostic factor” and for “primary tumour prognostic factor” concepts; fig.7 shows an example of definition of a prognostic factor (the HER2 growth factor receptor), of the related laboratory test (the immunoperoxidase test) and of the TNM stage. In TNM stage, an example of axioms appears.

In the following pages:

**Figure 4 :** The “is-a” hierarchy for the prognostic factor concept.

**Figure 5 :** The “is-a” hierarchy for the primary tumour prognostic factor concept

**Figure 6 :** Three examples of concept “leaves” of the concept hierarchy: the HER2 proto-oncogene, the Immunoperoxidase laboratory test and the TNM stage.

on whether we are looking for current properties of the breast cancer or whether we want to identify currently not observable states (i.e. past, present and future biological growing characteristics) of the breast cancer; in the first case, we should analyse breast cancer factors and determine a “stage” that is known to lead to a certain evolution of the disease; in the second case we should determine biological breast cancer history and evolution, by modelling the tumour activity and observing the biological characteristics of the disease. The first case corresponds to the task usually performed by oncologists during their work; the second case is the task more usually performed by researchers in cancer biology. The modern view of oncology joins the two cases, since nowadays the biological history of the tumour is more taken into account and prognosis is the consequence of analysing the interactions among “classical” prognostic parameters in relation to the biological activity of the tumour.

In the first case, following the cycle of patient management specified above and the suite of problem types in [16, chap.4], the management of breast cancer patient is the sequence of tasks shown in fig.2b. Connecting fig.2a and fig.2b, diagnosis includes initial diagnosis and its confirmation, assessment includes the evaluation of the disease (that is the stage considering certain prognostic factors and the associated prognosis), assignment includes the selection of therapy and monitoring includes the follow-up of the patient. With respect to this, prognosis is well distinguished from diagnosis: diagnosis is the task which establishes the presence or absence of the disease, while assessment determines its grade (stage) attribution. This parallels the approach normally adopted in clinical practice, in which normally the first step is diagnosis, and subsequently prognosis follows, possibly after further examinations. Moreover, monitoring is included in follow-up and it is not needed properly in prognosis; while prediction is not needed since the current stage of the disease (as well as a certain memory of the previously assessed ones) determines the proper therapy.

However, if we consider prognosis as a task in which the biological history of the cancer has to be reconstructed and predicted, the assessment task should be further specialised by the addition of a prediction task (fig.2c). In this case, the assignment of a therapy at a given instant is a parameter of the function which takes into account the global history - past, present and future - of the tumour (fig. 8). A proper therapy assignment should optimise the prediction in order to maximise some output parameter (such as, for example, the survival time); in this case, therapy is not a direct consequence of the stage of the disease, but it comes out from a sort of “propose and revise” task [16, chap.11], for example, by considering the identified states of the tumour history as different levels of abstraction of the disease. This optimization problem is not addressed in this work.

Moreover, diagnosis, prognosis, therapy and follow-up needs including new reliable research findings, but this is more perceived in prognosis. The knowledge which should update our guideline system for breast cancer prognosis also comes from an assessment task; that is, for example, after reading an article on breast cancer prognosis, it can be assessed that the presented results are reliable, maybe in contradiction with previous ones, that other previous results receive further sup-

Moreover, prognosis is not a task built upon static knowledge. A prognostic knowledge model should allow updating knowledge, by the introduction of new research results on prognostic factors. In this work, we do not intend to face the conceptualisation of knowledge extraction deeply, since it is anyway a process that is independent of prognosis, which is the objective of this work. The present model should be planned in order to allow the introduction of the output of this knowledge extraction process. So, while we assume that this knowledge extraction process is feasible (at least it is feasible to select the papers that deal with breast cancer prognosis with the help of a bibliographic research, i.e. by introducing proper keywords in a CD-ROM), we should provide both a “format” for this knowledge and the mechanism to allow for its insertion in the expert model.

Before starting with the description of the knowledge categories of the prognostic problem, it is worthwhile to check whether problem definitions already present in CommonKADS are also suitable for prognosis, in order to reuse elements of the CommonKADS modelling libraries that are already potentially modelled for breast cancer prognosis.

### **3.3.1. Definition of prognosis**

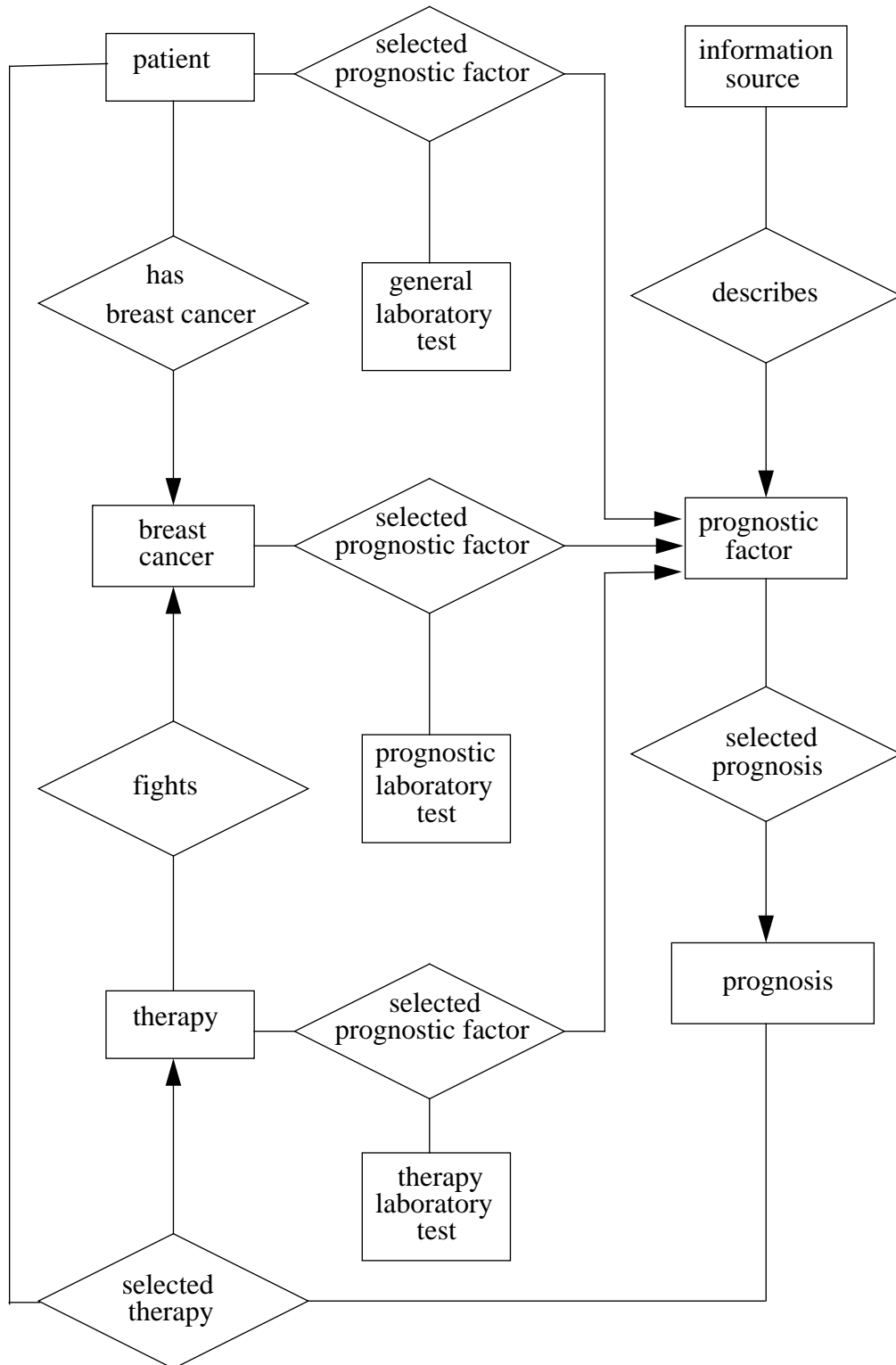
We used the term “prognosis” with the meaning of judgement - assessed by a physician after a diagnosis - of the duration of a disease and the prediction of its future behaviour; in our case, at least in terms of survival time (such as, for example, 5-year and 10-year classes) and tumour recurrence. With respect to this, it is clear that we are dealing with an analysis problem [16, chap.4], which includes prediction, monitoring, diagnosis and assessment. Prediction seems the best aspect, since “prediction” is intrinsic to the definition of the problem, that is prognosis as prediction of the behaviour of the tumour. Anyway also monitoring (since we are interested in an “on line prognosis”, that is, prognosis of a disease in a patient should be revised in time, specifically since we are considering long periods), diagnosis (since prognosis may be regarded as a more detailed diagnosis, that is, after a diagnosis of the disease, variables such as, for example, survival time should be estimated), and assessment (since a class/grade of the disease has to be identified) aspects may be considered as possible candidates for the application of the CommonKADS methodology.

### **3.3.2. Decomposition of prognosis in generic tasks**

In order to identify prognosis tasks, we decomposed patient management in order to verify whether it consists of a mixture of generic tasks. Since reusability is also addressed by CommonKADS, we have searched if the subtasks obtained were already defined in the CommonKADS library.

The prognostic task (“evaluation of the disease” in fig. 2a) is the crucial point of the patient management. The task definition of the prognostic task mainly depends

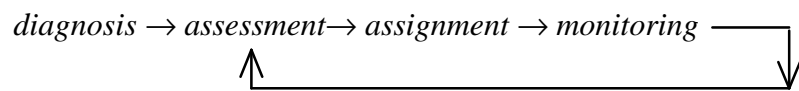




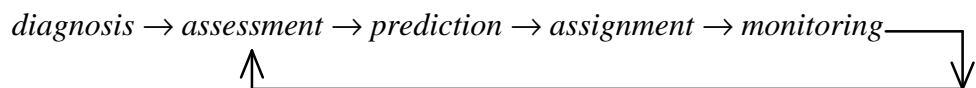
**Figure 3 :** The domain level at the root definition.

1.initial diagnosis  $\Rightarrow$  2.confirmation of diagnosis  $\Rightarrow$   
 3.evaluation of disease  $\Rightarrow$  4.selection of therapy  $\Rightarrow$  5. follow up

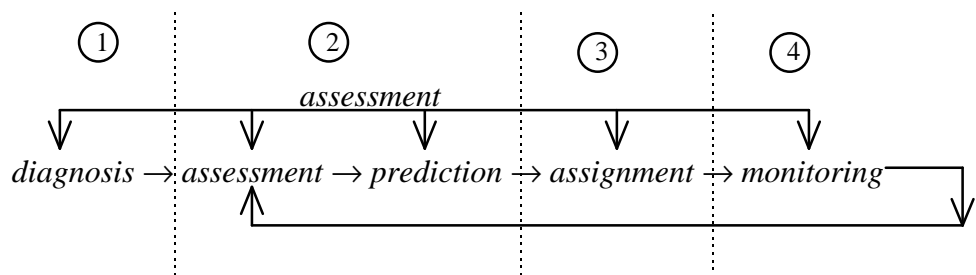
(a)



(b)



(c)



(d)

**Figure 2 :**

- (a) Breast cancer patient management.
- (b) Transferring of patient management to reusable tasks.
- (c) The modern trend of breast cancer oncology, regarding prognosis not only as a stage assessment, but as a prediction of the biological history of the tumour.
- (d) Updating of (c) tasks should be allowed, by extracting knowledge from literature, thus introducing an assessment task, which regards all the tasks of patient management, particularly the prognostic tasks.

- the task knowledge describes a recursive decomposition of a top-level task in sub-tasks, specifies these tasks, and describes when the subtasks are to be executed in order to achieve their parent task (control).

These descriptions are made by the CommonKADS Conceptual Modelling Language (CML) [18]. For many applications, these three layers are sufficient to build the system. Moreover, the CommonKADS modelling libraries capture knowledge engineering expertise in terms of reusable elements that are potentially modelled in a project. For example, the CommonKADS library of generic models offers models for diagnosis, design, planning, etc. These descriptions are made through the CommonKADS Conceptual Modelling Language (CML) [18].

### 3.2 The sources of experience

In our model, we deal with two types of knowledge:

- well assessed knowledge - which has already been included in prognostic guidelines - in order to produce the skeleton of the model for the prediction of the behaviour of breast cancer;
- new knowledge - which has not already been included in prognostic guidelines - in order to add new prognostic factors in the model.

In the first case, we followed the trace and the bibliography of the document “Breast Cancer” for physicians contained in the CancerNet Web info-server with PDQ (Physician Data Query) statements from National Cancer Institute USA (available at <http://biomed/nus.sg>). In the second case we should consider articles on breast cancer prognostic parameters taken from specialised journals.

Moreover, experts in oncology from IST (Genoa, Italy) have been consulted during the modelling construction process.

### 3.3 The general model

In order to transform the problem into a “well-defined” problem, we must find out how breast cancer prognosis is inserted in the patient management process. The management of breast cancer patients generally follows the task flow of fig.2a. In this work, we focus on the 3rd task. In general, 3rd, 4th and 5th tasks are iterated, that is the evaluation of the disease may be reassessed during follow-up, and therapy may be also reassessed in order to allow “ad hoc” changes in the selection of therapy; for example, after a surgical removal - which might be considered as an optional therapy (since it is not always necessary, although it is often performed) - an additional evaluation of the disease is certainly assessed.

### **3 Modelling breast cancer prognosis and treatment with CommonKADS**

#### **3.1 Conceptual modelling with CommonKADS**

Our approach to the conceptualisation of the problem follows the CommonKADS (Knowledge Acquisition and Design Structuring) Library for Expertise Modelling, as described in [16]. KADS is a comprehensive methodology for the development of knowledge based systems (KBS); KADS was set up during European research projects (ESPRIT P1098 and P5248) and is becoming a “de facto” standard for KBS development in Europe; KADS methodology is currently under evolution and CommonKADS is the name of the last version which was available at the beginning of this work.

A CommonKADS model is a set of interrelated models from the CommonKADS model set. This model set specifies six model templates to describe different views on, or models of, a problem solving context [16]. The six models are:

1. the Organisation Model, which describes the organisational context in which the knowledge based activities that the project is concerned with occur;
2. the Task Model, which describes the tasks and activities that are executed to realise the organisational function;
3. the Agent Model, which collects the relevant properties of the different agents performing the previous defined tasks;
4. the Communication model, which describes transactions between agents;
5. the Expertise Model, which describes the knowledge of an agent relevant to a particular task;
6. the Design Model, which describes the realisation of the problem solving behaviours described in the Expertise and Communication models in computational and representational terms.

In this work we address the CommonKADS Expertise Model. Expertise modelling is founded on the Newell’s notion of knowledge level [17]. In CommonKADS the different roles are captured in three basic independent knowledge categories [16]:

- the domain knowledge specifies form, structure and contents of the specific domain which is relevant for an application (structures described through concepts and relations);
- the inference knowledge specifies the primitive steps in reasoning (inferences) in an application and the knowledge roles that refer to classes of domain knowledge statements manipulated by the inferences;

Modelling Language) [18] allows a structural approach to conceptualisation. Thus, in our opinion, it is worthwhile to use CommonKADS for our aim. The model presented here has been built following CommonKADS methodology according to [16] and [18]; at this stage, we have not used any specific CommonKADS tool. Later on, we tested COKACE (**CommonKADS-Centaur**), a tool developed in the ACACIA group. This tool supports the building and validation of CommonKADS expertise models, described in CML. We used this tool for the construction of a simplified model which regards the treatment of breast cancer; this model has been reported in section 8 page 72 .

The aim of this part of work is to provide a preliminary conceptualisation of the breast cancer prognosis while evaluating the efficacy of the CommonKADS methodology in facing the problem. In this respect, we wanted to build a conceptual knowledge model (in CommonKADS referred to as model of expertise) of the breast cancer prognosis, that is an intermediate knowledge representation understandable by the human expert and by the knowledge engineer, thus enriching communication and leading gradually to a shared understanding of the emerging conceptual model of the domain [8], as well as improving explanation, documentation and maintenance of the application. The definition of a conceptual knowledge model may be further used for the development of an expert system on the prognosis of breast cancer; therapy will also be addressed in terms of prognostic factor.

### **2.3 Related works from bibliography**

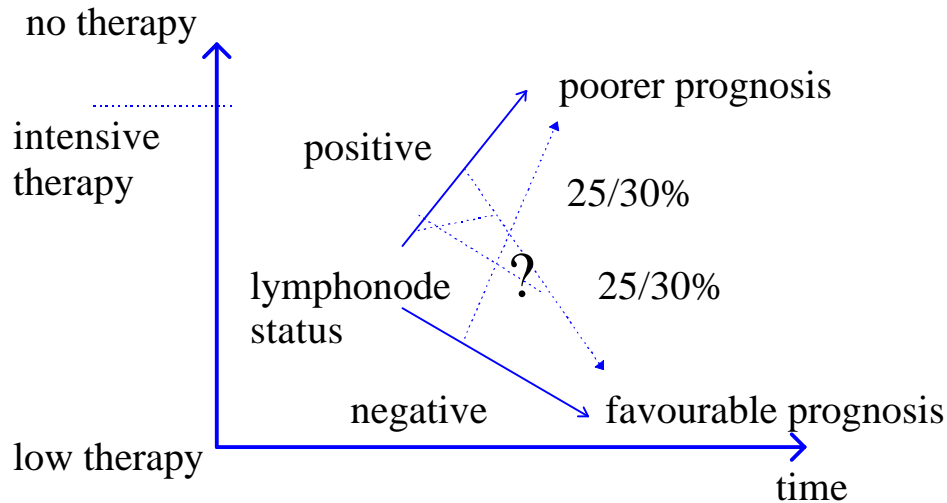
In literature, there are several examples of expert systems on oncology patient management and diagnosis, such as, for example, ONCOCIN [9, 10], BREASTCAN [11], INC2 [12], SENEX [13] and others [14, 15]. Most of them focus on guiding the treatment of patients according to well assessed protocols, whereas the aim of the present work focuses on well assessed and new prognostic factors (extracted from recent literature), in order to give a prediction of the behaviour of the tumour which allows for the administration of an appropriate therapy. In this respect, we are not, actually, interested in patient management, but rather in producing an “intelligent” information system, that is a system which is able to inform and guide the physician in the analysis of recent findings and guidelines on breast cancer prognosis.

KADS has already been used for cancer treatment modelling in K-ONCOCIN [19] (specifically of Northern California Group Protocol 2083-1 for small-cell lung carcinoma treatment in ONCOCIN [9, 10]). The results of the application of the KADS methodology in K-ONCOCIN were not completely satisfactory; for example, the library of interpretation models (general models in CommonKADS) did not provide an inference structure that they could have used to model their task, the model transformation in KADS was found to be a poorly understood process, that is the technique did not assist the developer in overcoming the bias and information loss that can occur during the model-transformation phases.

Our approach to the model development is quite different from K-ONCOCIN. For example, we started conceptual modelling by a knowledge acquisition process, while K-ONCOCIN started from previous computational models, that, according to the author, may have provided them with biased preconceptions [19]; in addition, our model focuses on prognosis and information aspects, while K-ONCOCIN addresses the complex task of administering cancer therapy; moreover, better results have been achieved in other application fields (such as, for example, KNOP [16, chap. 11] and the VT task [20]); finally, the introduction of the CommonKADS CML (Conceptual

ry of the tumour, in order to select carefully groups of patients with unfavourable prognosis.

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**Figure 1 :** Qualitative trend of breast cancer in function of the lymph node status of the primary tumour; positive status is likely to lead to a poorer prognosis while negative status is likely to lead to a favourable prognosis; 25/30% of the two categories of patients may have an opposite evolution.

A further problem originates by the fact that present day growth of cancer literature is of exponential nature (breast cancer is a typical example) [7]. Thousands of experimental and clinical researchers are actively engaged in cancer research. Specifically, one of the main aspects which is being increasingly investigated is the identification of prognostic factors for breast cancer, and specialised journals continuously report a flood of interesting results, at times conflicting; the evaluation of these results (whether, for example, there is not any bug due to the lack of some aspect of the research, or too much hurried conclusions) is also a very complex task which aims at producing a prognostic guideline.

In conclusion, the prognostic judgement, nowadays often constrained by rigid protocols, is likely to acquire a better flexibility in the near future, in order to face better the variability of breast cancer disease; in this case, a knowledge based system for prognostic decision which is able to manage a great amount of information will be certainly needed.

based system, but in our view, the most interesting application of this model is to be a base on which building guidelines from literature on cancer, in a future development.

## **2.2 Introduction to breast cancer prognosis and treatment**

Breast cancer is an extremely various disease, especially as relates to its evolution. The course of the disease ranges from cases characterised by rapid growth and tendency to metastasis to cases characterised by low growth generally with favourable prognosis. Although breast cancer stage determined by diagnosis is one of the most important prognostic factors, it is known that within neoplasia categories which may seem homogeneous for clinic-pathological parameters, cases with different evolution can be observed.

Lymph nodes state (positive, N+, vs. negative, N-) is one of the most important prognostic factors in breast cancer patients and the one which determines post-surgical treatment. Patient survival percentage after 5 years in the N- cases is about 67-85%; this value decreases if lymph node metastasis are found (N+) and the decrease depends on the number of lymph nodes involved in the pathological process [1-4]. The research effort towards other prognostic factors is mainly due to the fact that within the more favourable category (N-) there is a group (about 25-30%) with unfavourable prognosis (less than 10 years survival) [2, 3] and, in parallel, within the less favourable category (N+) there is a group (about 25-30%) with favourable prognosis (more than 10 years survival) [4] (fig.1); so it is likely that an inadequate therapy is adopted - specially an "undertreatment" in the N- cases [2,3] - following the present therapy protocols.

At present, one major research aspect is the identification of one or more prognostic factors accurate enough to define different therapeutic decisions. Prognosis and selection of therapy are mainly influenced by the age of the patient, stage of the disease, pathology features of the primary tumour including the presence of tumour necrosis, oestrogen-receptor (ER) and progesterone-receptor (PR) levels in the tumour tissue, and measures of proliferative capacity, as well as by menopausal status and general health. Besides, it has been found that these parameters are not sufficient to define a proper prognosis if they are considered separately.

So, nowadays research mainly directs its efforts towards a characterisation of the natural history of the tumour, in terms of biological parameters. The biologic parameters seem to be very promising even if they are currently in phase of study; for example, ER and PR [5] have already been identified as important prognostic factors. Good results are expected from other biological parameters, such as, for example, growth factor receptors like erbB-2 [6]. Each prognostic factor on its own is not sufficient for the prediction of the biological behaviour of the tumour; but a combination of these parameters is necessary, taking in mind (that is modelling) the natural histo-



## **2 Introduction to conceptual modelling in breast cancer**

### **2.1 Introduction to some oncologic problems**

Cancer is a group of more than 100 different diseases. Cancer occurs when cells become abnormal and keep dividing and forming more cells without control or order. All organs of the body are made up of cells. Normally, cells divide to produce more cells only when the body needs them. If cells divide when new ones are not needed, they form a mass of excess tissue, called a tumour. Tumours can be benign (not cancer) or malignant (cancer). The cells in malignant tumours can invade and damage nearby tissues and organs. Cancer cells can also break away from a malignant tumour and travel through the bloodstream or the lymphatic system to form new tumours in other parts of the body. The spread of cancer is called metastasis. Cancer is treated with surgery, radiation therapy, chemotherapy, hormone therapy, or biological therapy. The doctor may use one method or a combination of methods. The choice of treatment depends on the type and location of the cancer, whether the disease has spread, the patient's age and general health, and other factors. Many cancer patients take part in clinical trials (research studies) testing new treatment methods. Such studies are designed to improve cancer treatment.

Clinical practise guidelines are more and more developing in order to decrease the delays in implementation of research findings into practise for similar pathology conditions. This trend is particularly felt in cancer domain, where the decrease in mortality should be deeply influenced by making state-of-art knowledge and best medical practices applied to each cancer patient.

Literature review in oncology is a very complex task, as well as the boot for guidelines development. The central problem originates by the fact that present day growth of cancer literature is of exponential nature (breast cancer is a typical example). Specifically, one among the many aspects which are being increasingly investigated is the identification of prognostic factors for cancer and for breast cancer in particular (the more common cancer in women); the evaluation of the flood of, sometimes in conflict, results reported by specialised journals (whether, for example, there is not any bug due to the lack of some aspect of the research, or too much hurried conclusions) aims at producing a prognostic guideline.

Although knowledge organisation is rapidly changing in the last few years by the introduction of hypertext and multimedia techniques, the knowledge resulting from a research activity is likely to be still presented and recorded by the very authors in natural language (usually English) for many years. This does not exclude that an electronic format of the paper, that is of the journal in which the paper has been published, will be given for many journals in a brief time.

In this work, we aimed at producing a conceptual model of breast cancer prognosis and treatment. This conceptual model may be used for building a knowledge

## 1 Introduction

The research work reported has been carried out in the context of a post-doctoral scientific visit in the ACACIA project at the INRIA research centre in Sophia-Antipolis (France). The ACACIA (Acquisition des Connaissances pour l'Assistance à la Conception par Interaction entre Agents) project is a multidisciplinary project that aims at offering models / methods / tools in order to help the knowledge engineer to acquire knowledge from multiple expertise sources (experts and documents). ACACIA project is interested either in capitalizing knowledge on a given domain or in building an explanatory knowledge based system. The aim is to offer new generic models in order to help the knowledge engineer to interpret the expertise documents (for example obtained after elicitation sessions); such models focus on solving problems of multiple expertises and of explanatory knowledge acquisition. For representation of expertise models or of acquired knowledge, the formalism adopted is commonly in terms of conceptual graphs as well following the methodological framework offered by CommonKADS. Various research is being done on knowledge acquisition from multiple experts: collective elicitation protocol, model of cognitive agents for guiding knowledge acquisition, management and comparison of multiple viewpoints, detection and solving of conflicts among several expertise models, comparison of knowledge graphs, generation of consensual rules among experts, architecture of cognitive agent, extension of CommonKADS for multi-expertise and for multi-agent systems. The project also works on modelling explanation task and activity, on explanation evaluation and on the integration of explanatory knowledge acquisition into a knowledge acquisition method such as KADS. The documentation aspect is tackled through the exploitation of hypertext techniques for knowledge acquisition and explanations based on electronic documents.

Moreover, although the knowledge acquisition process has mainly regarded the analysis of documents (papers, books ...), the research work described in this report has also been supported, when needed, by experts from the IST (Institute for the Study on Tumours) from Genoa.

In the context of this research visit, there have been two main objectives:

- defining a preliminary expertise model for breast cancer prognosis and therapy;
- verifying the potentiality of the CommonKADS methodology to define an expertise model in the medical domain.

*Using CommonKADS to build an expertise model for breast cancer prognosis and therapy*5

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# **Utilisation de CommonKADS pour la construction d'un modèle d'expertise pour le pronostic et la thérapie du cancer du sein**

**Résumé :** L'un des principaux aspects de la recherche sur le cancer du sein est l'identification de paramètres pronostiques suffisamment exacts pour permettre d'organiser des stratégies thérapeutiques différenciées ; aucun facteur pronostique n'est suffisant seul pour prédire le comportement biologique d'une tumeur, mais une combinaison de tels paramètres est indispensable. En outre, la littérature sur le cancer, en particulier sur ses aspects biologiques, croît actuellement de façon exponentielle, et la gestion des connaissances dérivant de la recherche sur le cancer aurait besoin d'une conceptualisation de ces connaissances pour simplifier le processus de production de guides pour le pronostic et la thérapie du cancer.

Les travaux décrits dans ce rapport se sont focalisés sur la définition d'un modèle conceptuel des connaissances sur le pronostic et la thérapie du cancer du sein. Nous avons suivi la méthode CommonKADS et, en particulier, la bibliothèque offerte par CommonKADS pour la modélisation de l'expertise. Le but de ces travaux était de fournir une première conceptualisation du pronostic et la thérapie du cancer du sein, tout en évaluant l'efficacité de la méthode CommonKADS dans ce cadre.

**Mots-clé :** CommonKADS, acquisition de la connaissance, cancer du sein, domaine médical.

# Using CommonKADS to build an expertise model for breast cancer prognosis and therapy

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Programme 3 : Intelligence artificielle,  
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**Abstract:** One of the major aspects in breast cancer research is the identification of prognostic factors accurate enough to define different therapeutic decisions; each prognostic factor on its own is not sufficient for the prediction of the biological behaviour of the tumour, but a combination of these parameters is necessary. Moreover, nowadays growth of cancer literature, specifically on biological aspects, is of exponential nature, and the management of the knowledge deriving from cancer research needs a knowledge conceptualisation in order to simplify the process of guideline production in cancer prognosis and therapy. The work described here focuses on the definition of a conceptual knowledge model of the prognosis and the therapy of breast cancer. Our approach to the conceptualisation of the problem follows the CommonKADS (Knowledge Acquisition and Design Structuring) Library for Expertise Modelling. The aim of this work is to provide a first conceptualisation of breast cancer prognosis and therapy, while evaluating the efficacy of the CommonKADS methodology in facing the problem.

**Key-words:** CommonKADS, knowledge acquisition, breast cancer, medical domain.

*(Résumé : tsvp)*

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