Short term fasting, IGF/insulin-axis and therapy outcome in patients with cancer

Groot, S. de

Chapter 9

General discussion and future perspectives

Discussion

This chapter discusses the main findings of the studies described in the eight previous chapters in the context of the current literature. The thesis is divided into two parts as described in the introduction (**Chapter 1**); the first part focusses on the effects of short-term fasting on chemotherapy outcome in patients with breast cancer and the second part on the IGF-1 and insulin pathway as a target for cancer therapy and as a biomarker for chemotherapy outcome.

Part I. Short-term fasting and fasting mimicking diets as an adjunct to chemotherapy

In this part of the thesis the effects of short-term fasting and fasting mimicking diets on toxicity and efficacy of chemotherapy is investigated.

In **Chapter 2**, preclinical research is evaluated, which shows that short-term fasting during chemotherapy is effective in vitro in a wide variety of tumors, such as breast cancer, ovarian cancer, melanoma, lung cancer and colorectal cancer[1,2]. Moreover, data suggest that short-term fasting enhances the effects of radiotherapy and tyrosine kinase inhibitors (TKIs) as well[3-5]. Preclinical studies also show that short-term fasting simultaneously protects mice from chemotoxicity[1,6]. The mechanisms behind the distinctive response of healthy and cancer cells, which is described as "Differential Stress Resistance" (DSR), to short-term fasting are not fully unravelled[7,8]. However, it is clear that IGF-1 and insulin are important factors, as a decrease of these growth factors increase stress resistance in healthy cells to chemotherapy agents like doxorubicin or cyclophosphamide, but not in cancer cells[9]. Autophagy and glucose metabolism are also proposed mechanisms behind the DSR, due to nutrient deprivation, whereby tumors with diminished autophagy are highly sensitive to short-term fasting[7]. Although preclinical results are promising, the application of short-term fasting in cancer patients is not obvious. The metabolic differences between mice and humans for example may cause that humans need to fast for much longer periods to have similar effects as seen in mice[10]. Clinical research is in its infancy, however, the few small clinical studies to date show that short-term fasting as an adjunct to chemotherapy in humans is safe[11-15], as only mild side effects as hunger and dizziness were seen[12,14-16].

The effects of short-term fasting on chemotherapy-induced side effects and quality of life (QOL) in humans is not evident yet, however, there are some indications that patients may benefit. In a case series a reduction in fatigue, weakness, vomiting and diarrhea was seen when patients with distinct chemotherapy schedules fasted during the chemotherapy cycles compared to chemotherapy cycles without fasting[12]. Bauersfeld

et al. concluded that short-term fasting led to a better tolerance to chemotherapy with less compromised QOL and reduced fatigue in the 8 days following chemotherapy[15]. In another pilot trial from our hospital (**Chapter 3**), no difference in side effects were found, however, mean erythrocyte and thrombocyte counts 7 days post-chemotherapy were significantly higher in patients who fasted 24 hours before chemotherapy compared to patients in the control group[11]. In our DIRECT trial (**Chapter 4**), however, we found no difference in chemotherapy-induced side effects or QOL[16]. Moreover, the increase of levels of γ-H2AX in PBMCs, a marker of chemotherapy induced DNA damage in healthy cells, were lower in patients who fasted or used a fasting-mimicking diet compared to patients in the control group[11,14]. Reduction of side effects would improve QOL and potentially reduce expenses of hospitalization and the use of drugs such as anti-emetics. Moreover, short-term fasting may broaden the therapeutic window of cancer treatments, allowing for an increase of the dosage of (chemo) therapeutic agents, thereby enhancing their efficacy.

Although the effects of fasting on hormones and growth factors are studied in healthy subjects and it is known that glucose, insulin and IGF-1 levels decrease dramatically during short-term fasting[17-19], the exact effects of short-term fasting on these mediators in cancer patients during chemotherapy were unknown. In our pilot study we found evidence that during docetaxel, doxorubicin and cyclophosphamide (TAC) chemotherapy plasma glucose levels increased and insulin levels remained constant despite short-term fasting[11]. The use of concomitant dexamethasone for anti-emesis, reduction of fluid retention and dampening of hypersensitivity reactions in response to docetaxel may explain these findings, as it induces insulin resistance, compensatory hyperinsulinemia and hyperglycemia[20]. Therefore, the use of dexamethasone or other corticosteroids may counteract the beneficial impact of short-term fasting and fasting mimicking diets on chemotherapy tolerability and efficacy. In the DIRECT trial dexamethasone was omitted in the fasting mimicking diet arm during the first half chemotherapy cycles to reduce its potentially counteractive metabolic effects. As expected, a large decrease in insulin and glucose was found in the patients who were compliant to the fasting mimicking diet compared to the patients with a regular diet[16].

Preclinical studies show that chemotherapy efficacy can be enhanced by short-term fasting or fasting mimicking diets[1]. The first (small) clinical studies were predominantly focused on safety and the effects on chemotherapy-induced toxicity[11,15], although the effects on efficacy of chemotherapy may be more interesting. In the randomized DIRECT study, we found the first evidence of increased efficacy as a result of a fasting mimicking diet on radiological and pathological response according Miller and Payne in early breast cancer patients treated with doxorubicin, cyclophosphamide followed by docetaxel (AC-T) or 5-FU, epirubicin, cyclophosphamide followed by docetaxel (FEC-T). However, the,

pathological complete response after neo-adjuvant chemotherapy (Miller and Payne 5), was not different between the fasting mimicking diet group and the control group. Data on survival are not available yet[16]. Therefore, more research is needed to establish the effects of short-term fasting on chemotherapy efficacy and to research in which tumors short-term fasting may be effective as an adjunct to cancer treatment.

In the DIRECT study, the compliance to follow a 72-hour fasting mimicking diet during the chemotherapy cycles was high for 1 cycle but decreased with subsequent cycles. In other (small) studies usually a higher compliance rate for 3 or more cycles is seen[12,15]. The disappointing compliance rate in the DIRECT study may be caused by aversion to distinct components of the diet in combination chemotherapy, the amount of chemotherapy cycles and lacking support by a dietician which was not standard offered. Therefore, close monitoring of patients by nutritionists with expertise in low calorie diets may increase compliance. As well as diets with a more variable and fresh taste may be needed to increase compliance and successfully examine the impact on chemotherapy tolerability and efficacy. Although, one or two cycles of short-term fasting may be enough to increase efficacy of chemotherapy as seen in preclinical studies[1]. Additionally, ketone bodies measurements in urine appeared to be a good objective marker for compliance.

An important remark on safety is that effects of short-term fasting in patients at risk for malnutrition or cachexia are unknown and further limitation of nutrient intake in these patients may be unsafe, even for a short period of time. However, in fit patients, with a normal or high BMI treated with (neo)-adjuvant chemotherapy and without diabetes mellitus, short-term fasting emerges as a promising strategy to enhance the efficacy and tolerability of chemotherapy and more research is needed to firmly establish clinical effects.

Part II. IGF-1 and insulin pathway in cancer treatment

In the second part of the thesis the IGF-1 and insulin pathway in cancer treatment are investigated as a target for therapy and its predictive role. First, **Chapter 5** describes the IGF-1 pathway as an treatment target[21] and subsequently describes the pathway as biomarker for chemotherapy efficacy[21-23].

Clinical research of IGF-1R inhibitors has shown that IGF-1R inhibitors have no convincing benefit in clinical studies, except for a few patients with Ewing sarcoma[24,25]. We hypothesize that the failure of IGF-1R inhibitors in clinical studies may be caused by the complexity of the IGF-1R pathway. The pathway activation is not adequately inhibited by the distinct inhibitors, as IGF-1R inhibition causes hyperglycemia and subsequent hyperinsulinemia due to cross-reactivity with the insulin receptor isoform B (IR-B) and hybrid receptors and the ligand IGF-2 is not inhibited as well [21].

Therefore, the ligands insulin and IGF-2 still activate IR-A and hybrid receptors and stimulate tumor proliferation and survival via the same downstream pathway[26,27]. Additionally, in our preclinical experiments we found evidence that insulin causes resistance to IGF-1 inhibition, as it exhibits proliferative and survival effects in Ewing cell lines[21]. Therefore, activation of the IGF-1/insulin pathway through insulin could be an important resistance mechanism. Lowering insulin, perhaps with a short-term fasting intervention, or blocking its activity entirely with an IR-A inhibitor serves as a possible target in cancer therapy and may be effective in combination with IGF-1R inhibition[7,28]. Moreover, measuring biomarkers, such as ligand levels and receptor expression seems necessary to select patients who may benefit from treatment with IGF-1R inhibitors and urge for further research.

In **Chapter 6** we aimed to identify single nucleotide polymorphisms (SNPs), which influence the IGF-1R pathway activity, to predict chemotherapy efficacy in patients with HER2 negative early breast cancer treated in the NEOZOTAC trial. We found that variation in the *IGF-1R* gene was associated with pathological response, which may be explained by diminished IGF-1R activity [22]. Additionally, we evaluated if pathological response according Miller and Payne could be predicted by IGF-1R expression in the tumor before and after TAC chemotherapy in the same cohort [22]. A decline of IGF-1R expression in the tumor during treatment was associated with a better pathological response, in line with the study of Heskamp et al. where downregulation of IGF-1R during chemotherapy treatment was associated with prolonged survival[29]. Therefore, the IGF-1R seems to play an important role in therapy resistance in breast cancer patients. However, in our cohort diminished IGF-1R expression during treatment was not associated with better survival. (**Chapter 7**).

Additionally, in a small side study of the NEOZOTAC trial lower serum insulin levels were associated with improved disease-free survival [30]. Accordingly, Feroni et al. found that patients with breast cancer with higher levels of insulin had an increased risk for disease progression [31] and Goodwin et al. found that higher fasting insulin levels at baseline in breast cancer patients without diabetes were associated with worse overall survival [32]. Higher insulin levels may give the tumor a growth advantage by activating the IGF-1/insulin pathway [33].

The last chapter of this thesis (**Chapter 8**) describes how high baseline IGF-1 serum levels were associated with improved event-free survival and a trend for overall survival in patients with Ewing sarcoma treated with VIDE chemotherapy. Although counterintuitive, low levels of IGF-1 may reflect an endocrine adaptation to severe disease [34]. Supporting results for this hypothesis are for example that low levels of IGF-1 were associated with more aggressive systemic illness in Ewing sarcoma [35] and that lower

levels of IGF-1 were found in patients with metastatic disease compared to patients with localized disease [35]. Moreover, low levels of circulating IGF-1 predicted worse survival in other solid tumors [36-43] and systemic diseases [44,45] as well.

Additionally, serum IGF-1 levels may have little or no influence on tumor growth, as the autocrine production of IGF-1 (and IGF-2/insulin) is probably sufficient and decisive in most patients with Ewing sarcoma [46-49]. Therefore, determining of autocrine IGF-1 (and IGF-2/insulin) levels as well as the expression of the IGF-1R in the tumor might help to select patients who could benefit from (co-) treatment with an IGF-1R inhibitor.

Conclusion and future perspectives

Although the first small clinical studies of short-term fasting as adjunct to chemotherapy are promising in terms of decreased toxicity and enhanced efficacy [15,16,50], the exact mechanism and effects are not established yet. Besides, it has not been proven that short-term fasting provokes a better overall survival. More studies and a longer follow-up are needed to prove this. Therefore, fasting interventions should only be applied in the context of clinical research in patients with cancer until there is robust evidence for the safety and benefits. For future studies some recommendations can be done. First, tumors in which insulin or IGF-1 pathway are known to cause chemotherapy resistance, such as breast cancer [22,29,51], may be good candidates for future studies of short-term fasting as an adjunct to chemotherapy. Second, an adequate decrease in insulin, glucose and IGF-1 are probably needed to have beneficial effects on treatment outcome, thus the fasting intervention should have an adequate length. The 72-hour fasting mimicking diet used in the DIRECT study seems an good approach as insulin decreased dramatically, however, the compliance was unexpectedly low [16]. Therefore, in future studies more variable diet options and close monitoring of patients by nutritionists with expertise in fasting may be needed. Besides fasting interventions to increase tolerability and efficacy of chemotherapy, future studies should also address other therapies as targeted therapy and immunotherapy. Another approach for future studies may be to combine short-term fasting with physical therapy, as exercise during chemotherapy can improve treatment outcome as well and increase muscle strength and patients quality of life[52-54]. Additionally, as there is increasing evidence that hyperglycemia and hyperinsulinemia worsen the outcome in cancer patients [55], the wide-use of corticosteroids during chemotherapy may be debated [56] and studies as the REDEX trial (NCT02776436), to decrease the use of these agents may be of huge interest. Moreover, the disappointing results of clinical studies of IGF-1R inhibitors may be caused by the complexity of the IGF-1R pathway, whereby pathway activation is not adequately inhibited due to the ligands insulin and IGF-2 and activation of IR-A. Therefore, good strategies for future research would be to combine IGF-1R inhibition with IR-A inhibition and/or lowering insulin with short term fasting, based on biomarkers and ligand levels.

References

1. Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Sci Transl Med. 2012;4(124):124ra27.
2. Shim HS, Wei M, Brandhorst S, Longo VD**.** Starvation promotes REV1 SUMOylation and p53-dependent sensitization of melanoma and breast cancer cells. Cancer Res. 2015;75(6):1056-67.
3. Safdie F, Brandhorst S, Wei M, Wang W, Lee C, Hwang S, et al. Fasting enhances the response of glioma to chemo- and radiotherapy. PLoS. One. 2012;7(9):e44603.
4. Saleh AD, Simone BA, Palazzo J, Savage JE, Sano Y, Dan T, et al. Caloric restriction augments radiation efficacy in breast cancer. Cell Cycle. 2013;12(12):1955-63.
5. Caffa I, Longo VD, Nencioni A**.** Fasting plus tyrosine kinase inhibitors in cancer. Aging (Albany. NY). 2015;7(12):1026-7.
6. Tinkum KL, Stemler KM, White LS, Loza AJ, Jeter-Jones S, Michalski BM, et al. Fasting protects mice from lethal DNA damage by promoting small intestinal epithelial stem cell survival. Proc. Natl. Acad. Sci. U. S. A. 2015;112(51):E7148-E54.
7. de Groot S, Pijl H, van der Hoeven JJM, Kroep JR**.** Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019;38(1):209.
8. Nencioni A, Caffa I, Cortellino S, Longo VD**.** Fasting and cancer: molecular mechanisms and clinical application. Nature Reviews Cancer. 2018;18(11):707-19.
9. Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, Parrella E, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. Cancer Res. 2010;70(4):1564-72.
10. Jensen TL, Kiersgaard MK, Sorensen DB, Mikkelsen LF**.** Fasting of mice: a review. Lab Anim. 2013;47(4):225-40.
11. de Groot S, Vreeswijk MP, Welters MJ, Gravesteijn G, Boei JJ, Jochems A, et al. The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study. BMC Cancer. 2015;15:652.
12. Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, et al. Fasting and cancer treatment in humans: A case series report. Aging (Albany. NY). 2009;1(12):988-1007.
13. T B, A I, A A**.** Safety and Feasability of Muslim Fasting While Receiving Chemotherapy. IOSR Journal of Pharmacy. 2014.
14. Dorff TB, Groshen S, Garcia A, Shah M, Tsao-Wei D, Pham H, et al. Safety and feasibility of fasting in combination with platinum-based chemotherapy. BMC Cancer. 2016;16:360.
15. Bauersfeld SP, Kessler CS, Wischnewsky M, Jaensch A, Steckhan N, Stange R, et al. The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. BMC Cancer. 2018;18(1):476.
16. S de Groot RL, MJ Welters, I Ehsan, MP Vreeswijk, VT Smit, H de Graaf, JB Heijns, JE Portielje, AJ van de Wouw, AL Imholz, LW Kessels, S Vrijaldenhoven, A Baars, E Meershoek-Klein Kranenbarg, M Duijm-de Carpentier, E van Leeuwen-Stok, H Putter, VD Longo, JJ van der Hoeven, JW

Nortier, H Pijl and JR Kroep**.** Abstract P1-15-20: DIetary REstriction as an adjunct to neoadjuvant ChemoTherapy for HER2-negative breast cancer: Final results from the DIRECT trial (BOOG 2013-04). American Association for Cancer Research. 2019.

17. Cahill G, Jr., Felig P, Owen O, Wahren J**.** Metabolic adaptation to prolonged starvation in man. Nord. Med. 1970;83(3):89.
18. Thissen JP, Ketelslegers JM, Underwood LE**.** Nutritional regulation of the insulin-like growth factors. Endocr. Rev. 1994;15(1):80-101.
19. Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A**.** Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PLoS One. 2019;14(1):e0209353.
20. Hickish T, Astras G, Thomas P, Penfold S, Purandare L, Hickish TF, et al. Glucose intolerance during adjuvant chemotherapy for breast cancer. J Natl Cancer Inst. 2009;101(7):537.
21. Stefanie de Groot KS, Bas T. Röttgering, Hans Gelderblom, Hanno Pijl, Judith R. Kroep**.** Unravelling the resistance of IGF-pathway inhibition in Ewing sarcoma and breast cancer. In preparation.
22. de Groot S, Charehbili A, van Laarhoven HW, Mooyaart AL, Dekker-Ensink NG, van de Ven S, et al. Insulin-like growth factor 1 receptor expression and IGF1R 3129G > T polymorphism are associated with response to neoadjuvant chemotherapy in breast cancer patients: results from the NEOZOTAC trial (BOOG 2010-01). Breast Cancer Res. 2016;18(1):3.
23. de Groot S, Gelderblom H, Fiocco M, Bovee JV, van der Hoeven JJ, Pijl H, et al. Serum levels of IGF-1 and IGF-BP3 are associated with event-free survival in adult Ewing sarcoma patients treated with chemotherapy. Onco Targets Ther. 2017;10:2963-70.
24. Olmos D, Postel-Vinay S, Molife LR, Okuno SH, Schuetze SM, Paccagnella ML, et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. Lancet Oncol. 2010;11(2):129-35.
25. Qu X, Wu Z, Dong W, Zhang T, Wang L, Pang Z, et al. Update of IGF-1 receptor inhibitor (ganitumab, dalotuzumab, cixutumumab, teprotumumab and figitumumab) effects on cancer therapy. Oncotarget. 2017;8(17):29501-18.
26. Djiogue S, Nwabo Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, et al. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer. 2013;20(1):R1-R17.
27. Ryu TY, Park J, Scherer PE**.** Hyperglycemia as a risk factor for cancer progression. Diabetes Metab J. 2014;38(5):330-6.
28. Pasanisi P, Bruno E, Venturelli E, Morelli D, Oliverio A, Baldassari I, et al. A Dietary Intervention to Lower Serum Levels of IGF-I in BRCA Mutation Carriers. Cancers (Basel). 2018;10(9).
29. Heskamp S, Boerman OC, Molkenboer-Kuenen JD, Wauters CA, Strobbe LJ, Mandigers CM, et al. Upregulation of IGF-1R expression during neoadjuvant therapy predicts poor outcome in breast cancer patients. PLoS.One. 2015;10(2):e0117745.
30. de Groot S, Pijl H, Charehbili A, van de Ven S, Smit V, Meershoek-Klein Kranenbarg E, et al. Addition of zoledronic acid to neoadjuvant chemotherapy is not beneficial in patients with HER2-negative stage II/III breast cancer: 5-year survival analysis of the NEOZOTAC trial (BOOG 2010-

01). Breast Cancer Res. 2019;21(1):97.

31. Ferroni P, Riondino S, Laudisi A, Portarena I, Formica V, Alessandroni J, et al. Pretreatment Insulin Levels as a Prognostic Factor for Breast Cancer Progression. Oncologist. 2016;21(9):1041-9.
32. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol. 2002;20(1):42-51.
33. Renehan AG, Zwahlen M, Minder C, O'dwyer ST, Shalet SM, Egger M**.** Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004;363(9418):1346-53.
34. Schumacher B, Garinis GA, Hoeijmakers JH**.** Age to survive: DNA damage and aging. Trends Genet. 2008;24(2):77-85.
35. Scotlandi K, Manara MC, Serra M, Marino MT, Ventura S, Garofalo C, et al. Expression of insulin-like growth factor system components in Ewing's sarcoma and their association with survival. Eur.J.Cancer. 2011;47(8):1258-66.
36. Shao YY, Huang CC, Lin SD, Hsu CH, Cheng AL**.** Serum insulin-like growth factor-1 levels predict outcomes of patients with advanced hepatocellular carcinoma receiving antiangiogenic therapy. Clin. Cancer Res. 2012;18(14):3992-7.
37. Elmashad N, Ibrahim WS, Mayah WW, Farouk M, Ali LA, Taha A, et al. Predictive value of serum insulin-like growth factor-1 in hepatocellular carcinoma. Asian Pac.J.Cancer Prev. 2015;16(2):613-9.
38. Kaseb AO, Morris JS, Hassan MM, Siddiqui AM, Lin E, Xiao L, et al. Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothelial growth factor in patients with hepatocellular carcinoma. J.Clin.Oncol. 2011;29(29):3892-9.
39. Tas F, Karabulut S, Bilgin E, Tastekin D, Duranyildiz D**.** Clinical significance of serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) in patients with breast cancer. Tumour.Biol. 2014;35(9):9303-9.
40. Tas F, Karabulut S, Serilmez M, Ciftci R, Duranyildiz D**.** Clinical significance of serum insulin-like growth factor-1 (IGF-1) and insulinlike growth factor binding protein-3 (IGFBP-3) in patients with epithelial ovarian cancer. Tumour.Biol. 2014;35(4):3125-32.
41. Cho EJ, Lee JH, Yoo JJ, Choi WM, Lee MJ, Cho Y, et al. Serum insulin-like growth factor-I level is an independent predictor of recurrence and survival in early hepatocellular carcinoma: a prospective cohort study. Clin Cancer Res. 2013;19(15):4218-27.
42. Gallego R, Codony-Servat J, Garcia-Albeniz X, Carcereny E, Longaron R, Oliveras A, et al. Serum IGF-I, IGFBP-3, and matrix metalloproteinase-7 levels and acquired chemo-resistance in advanced colorectal cancer. Endocr.Relat Cancer. 2009;16(1):311-7.
43. Huang YF, Cheng WF, Wu YP, Cheng YM, Hsu KF, Chou CY**.** Circulating IGF system and treatment outcome in epithelial ovarian cancer. Endocr.Relat Cancer. 2014;21(2):217-29.
44. Watanabe S, Tamura T, Ono K, Horiuchi H, Kimura T, Kita T, et al. Insulin-like growth factor axis (insulin-like growth factor-I/insulin-like growth factor-binding protein-3) as a prognostic predictor of heart failure: association with adiponectin. Eur.J.Heart Fail. 2010;12(11):1214-22.
45. Jia T, Gama AT, Heimburger O, Barany P, Lindholm B, Stenvinkel P, et al. IGF-1 and survival in

ESRD. Clin.J.Am.Soc.Nephrol. 2014;9(1):120-7.

46. Benini S, Zuntini M, Manara MC, Cohen P, Nicoletti G, Nanni P, et al. Insulin-like growth factor binding protein 3 as an anticancer molecule in Ewing's sarcoma. Int.J.Cancer. 2006;119(5):1039-46.
47. Yee D, Favoni RE, Lebovic GS, Lombana F, Powell DR, Reynolds CP, et al. Insulin-like growth factor I expression by tumors of neuroectodermal origin with the t(11;22) chromosomal translocation. A potential autocrine growth factor. J.Clin.Invest. 1990;86(6):1806-14.
48. Yee D, Paik S, Lebovic GS, Marcus RR, Favoni RE, Cullen KJ, et al. Analysis of insulin-like growth factor I gene expression in malignancy: evidence for a paracrine role in human breast cancer. Mol Endocrinol. 1989;3(3):509-17.
49. Scotlandi K, Benini S, Sarti M, Serra M, Lollini PL, Maurici D, et al. Insulin-like growth factor I receptor-mediated circuit in Ewing's sarcoma/peripheral neuroectodermal tumor: a possible therapeutic target. Cancer Res. 1996;56(20):4570-4.
50. de GS, Vreeswijk MP, Welters MJ, Gravesteijn G, Boei JJ, Jochems A, et al. The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study. BMC. Cancer. 2015;15:652.
51. Casa AJ, Dearth RK, Litzenburger BC, Lee AV, Cui X**.** The type I insulin-like growth factor receptor pathway: a key player in cancer therapeutic resistance. Front Biosci. 2008;13:3273-87.
52. Irwin ML, McTiernan A, Manson JE, Thomson CA, Sternfeld B, Stefanick ML, et al. Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. Cancer Prev Res (Phila). 2011;4(4):522-9.
53. Spei ME, Samoli E, Bravi F, La Vecchia C, Bamia C, Benetou V**.** Physical activity in breast cancer survivors: A systematic review and meta-analysis on overall and breast cancer survival. Breast. 2019;44:144-52.
54. Kapila AK, Hamdi M, Patel A**.** Clinicians Should Actively Promote Exercise in Survivors of Breast Cancer. Clin Breast Cancer. 2018;18(5):e747-e9.
55. Jiralerspong S, Kim ES, Dong W, Feng L, Hortobagyi GN, Giordano SH**.** Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. Ann Oncol. 2013;24(10):2506-14.
56. Ioannidis JP, Hesketh PJ, Lau J**.** Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol. 2000;18(19):3409-22.