EUROPEAN Journal of Medicine

Has been issued since 2013.
ISSN 2308-6513. E-ISSN 2310-3434
2016. Vol.(14). Is. 4. Issued 4 times a year

The journal is registered by Federal Service for Supervision of Mass Media, Communications and Protection of Cultural Heritage (Russian Federation). Registration Certificate **PI № FS 77 – 54156** 17.05.2013.

Journal is indexed by: **CAS Source Index** (USA), **CiteFactor** (Canada), **CrossRef** (UK), **EBSCOhost Electronic Jornals Service** (USA), **Electronic scientific library** (Russia), **Global Impact Factor** (Australia), **Journal Index** (USA), **Open Academic Journals Index** (Russia), **ResearchBib** (Japan), **Sherpa Romeo** (Spain), **The University of Melbourne Library Catalogue** (Australia), **ULRICH's WEB** (USA).

All manuscripts are peer reviewed by experts in the respective field. Authors of the manuscripts bear responsibility for their content, credibility and reliability.
Editorial board doesn't expect the manuscripts' authors to always agree with its opinion.

Postal Address: 26/2 Konstitutcii, Office 6
354000 Sochi, Russian Federation

Website: http://ejournal5.com/
E-mail: ejm2013@mail.ru

Founder and Editor: Academic Publishing House *Researcher*

Passed for printing 16.12.16.
Format 21 × 29,7/4.

Headset Georgia.
Ych. Izd. l. 4,5. Ysl. pech. l. 4,2.

Order № 14.

European Journal of Medicine

2016
№ 4

EUROPEAN Journal of Medicine

European Journal of Medicine

2016

№ 4

Издается с 2013 г.
ISSN 2308-6513. E-ISSN 2310-3434
2016. № 3 (13). Выходит 4 раза в год.

Журнал зарегистрирован Федеральной службой по надзору в сфере массовых коммуникаций, связи и охраны культурного наследия (Российская Федерация). Свидетельство о регистрации средства массовой информации **ПИ № ФС 77 – 54156** 17.05.2013.

Журнал индексируется в: **CAS Source Index** (США), **CiteFactor** (Канада), **CrossRef** (Великобритания), **EBSCOhost Electronic Journals Service** (США), **Global Impact Factor** (Австралия), **Journal Index** (США), **ResearchBib** (Япония), **Научная электронная библиотека** (Россия), **Open Academic Journals Index** (Россия), **Sherpa Romeo** (Испания), **ULRICH's WEB** (США).

Адрес редакции: 354000, Россия, г. Сочи, ул. Конституции, д. 26/2, оф. 6
Сайт журнала: http://ejournal5.com/
E-mail: ejm2013@mail.ru

Учредитель и издатель: ООО «Научный издательский дом "Исследователь"» - Academic Publishing House *Researcher*

Подписано в печать 16.12.16.
Формат 21 × 29,7/4.

Гарнитура Georgia.
Уч.-изд. л. 4,5. Усл. печ. л. 4,2.
Заказ № 14.

CONTENTS

Published in the Russian Federation
European Journal of Medicine
Has been issued since 2013.
ISSN: 2308-6513
E-ISSN: 2310-3434
Vol. 14, Is. 4, pp. 91-99, 2016

DOI: 10.13187/ejm.2016.14.91
www.ejournal5.com

UDC 616.6

Fibroblast Growth Factor 23: Review of its role in Clinical Medicine

Athena Myrou [a, *], Theodoros Aslanidis [b], Dimitrios Grekas [c]

[a] Internal medicine- Intensive Care Medicine, Thessaloniki, Greece
[b] Anesthesiology- Intensive Care Medicine,
National Center of Emergency Care, Thessaloniki Department, Greece
[c] School of Medicine, Aristotle University, Thessaloniki, Greece

Abstract

In the last decade, there is an ongoing interest about Fibroblast growth factor – 23. Its clinical significance seems to go far beyond hereditary disease. The current review presents the newest findings about this factor in several fields of medicine.

Along with its undoubted place in hereditary bone diseases and renal failure, in every stage, FGF23 role is far beyond clear. Further studies are needed to determine its place as prognostic, diagnostic or severity biomarker.

Keywords: Fibroblast Growth Factor 23.

1. Introduction

The FGF family

Fibroblast growth Factors (FGFs) are multifunctional proteins with a wide variety of effects; their role as biological signal facilitates a myriad of biological activities, ranging from issuing developmental cues (mesoderm induction, anterior-posterior patterning, limb development, and neural induction and development), maintaining tissue homeostasis, regulating metabolic processes, including keratinocyte organisation and wound healing. That's why; they often referred to as 'promiscuous growth factors (Finklestein, Plomaritoglou, 2001; Olsen et al., 2003).

The first discovery of FGF was made by Armelin in 1973. Today we know 22 structure-related signaling molecules in humans; thus, we are referring to them as FGF family. Today, FGFs are classified as intracrine, paracrine, and endocrine FGFs by their action mechanisms (Itoh et al., 2015). Paracrine and endocrine FGFs, which comprise 15 and 3 FGFs, respectively, are secreted signaling proteins. In contrast, intracrine FGFs, which comprise four FGFs, are intracellular proteins that are not functionally related to paracrine or endocrine FGFs. Endocrine FGFs comprise FGF19, FGF21, and FGF23. Members FGF1 through FGF10 all bind fibroblast growth factor receptors (FGFRs). Others (FGF11, FGF12, FGF13, FGF18) also known as FGF homologous factors 1-4 (FHF1-FHF4) or "iFGF", do not bind FGFRs and are involved in intracellular processes unrelated to the FGFs (Itoh, Ornitz, 2008); human FGF18 is involved in cell development and

* Corresponding author
E-mail addresses: taniamyrou@gmail.com (A. Myrou), thaslan@hotmail.com (T. Aslanidis), dgrekas@auth.gr (D. Grekas)

morphogenesis in various tissues including cartilage; human FGF20 was identified based on its homology to *Xenopus* FGF-20 (XFGF-20), etc.

1. This article focuses on FGF2-3: a molecule that is gaining more and more interest since its discovery, in 2000 (Pubmed search on "FGF23"/Fibroblast growth factor 23" retrieves 105 publications before 2000 and 980 from 2000-2015, search date 05/01/2016) (Itoh, Ornitz, 2004; Yamashita et al., 2000; Amin, 2014). The article reviews in brief, his structure and attempts to analyze its physiological and pathophysiological role.

2. Results

I. Structure and physiological role

Several tissues express FGF-23, such as bone tissue, bone marrow vessels, ventrolateral thalamic nucleus, thymus, and lymph nodes (Liu et al., 2003). Yet, the high levels of expression by osteocytes suggest that the bone tissue is the major source of FGF-23 (Liu, Quarles, 2007). The latter is a 32KD protein (251 amino acids), encoded in *FGF23 gene*, which in turn is located in chromosome 12p13 and composed by three exons (Amin, 2014). The protein contains a 24 starting signal amino acid peptid, an N-terminal region that contains the FGF homology domain (156 amino acids) and a novel 71–amino acid C-terminus (originally discovered by homology-based PCR screening of a mouse embryonic cDNA library), while the gene is phylogenetically grouped with FGF-19 and -21 gene products (Liu, Quarles, 2007).

2. FGF interacts with one of a family of four FGF receptors (FGFR, especially FGFR1c, 3c and 4c) that belong to type I transmembrane phosphotyrosine kinase receptors. Nevertheless, receptor activation needs a signaling complex formed by FGF, FGFR and Heparan sulfate proteoglycan (HSPG) which acts as a co-factor (Ornitz, 2000; Urakawa, 2006; Yu et al., 2005). Another signle-pass transmembrane protein, known as Klotho, is also required for FGF-23-induced receptor activation. Moreover, Klotho-FGFR coexpression seems to define tissue specificity (presence in kidney, parathyroid gland, pituitary gland and choroid plexus, absence in bone, lung, liver, skin, spleen) (Liu, Quarles, 2007).

As mentioned before, FGF-23 belongs *structurally* to FGF family. Yet, it is *functionally* included in a group of molecules called phosphatonins. Phophatonins are hormones that regulate phosphorus metabolism. sFRP-4 and MEPE (matrix extracellular Phosphoglycoprotein) are the other members of the group.

Regarding FGF-23, its principal target is kidney, where it regulates phosphate reabsorption and production of 1,25(OH)2D (Liu, Quarles, 2007). FGF23 inhibits both sodium-dependent phosphate reabsorption (by suppression of type 2a and 2c sodium-phosphate cotransporters expression) and 25-hydroxyvitamin D [25(OH)D]-1α-hydroxylase, while enhancing the expression of 25(OH)D-24-hydroxylase, in the proximal tubule. Thus, it causes phosphaturia leading to hypophosphatemia, and aberrant production and inappropriately low levels of 1,25(OH)2D (Shimada et al., 2004).

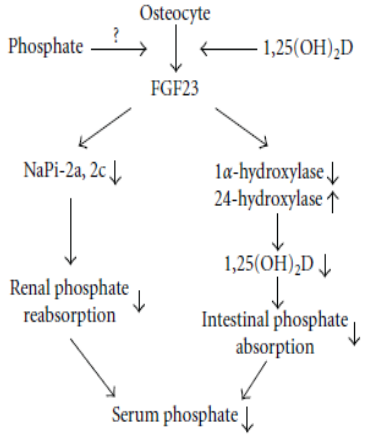

Fig. 1. Actions of FGF-23 (Saito, Fukumoto, 2009) (explanation see text)

The parathyroid gland is another target for FGF23, where it inhibits secretion of parathyroid hormone (PTH) (Shimada et al., 2004). On the other hand, direct action of FGF-23 on bones, its effect on pituitary gland and also in brain (where it is produced by ventrolateral thalamic nucleus) are not completely explored.

II. Clinical significance

1. Hereditary diseases

FGF23 disturbances are met in several hereditary diseases. In general, they are classified in two ways: a) syndromes of FGF23 excess and syndromes of FGF23 deficiency; and b) hypophosphatemic and hypephosphatemic disorders.

Autosomal Dominant Hypophospatemic Rickets (ADHR) (OMIM entry 193100...).

(ICD-10 E83.3, Phenotype MIM number 193100, gene FGF23, locus 12p13.32,). ADHR is a rare (less than 100 cases are described) familial disease, characterized by isolated renal phosphate wasting, hypophosphatemia, and inappropriately normal 1,25-dihydroxyvitamin D3 levels. Patients frequently present with bone pain, rickets, and tooth abscesses. Three heterozygous missense mutations around the processing site of FGF23 protein have been identified in ADHR families. These mutations replace 176Arg or 179Arg in FGF23 protein with other amino acids destroying R-X-X-R furin like cleavage domain motif. Therefore, it has been presumed that the cleavage of FGF23 protein between 179Arg and 180Ser is prevented by these mutations causing increased full-length FGF23 level. Cleaved FGF23 forms due to intracellular proteolysis lose their biological activities. *FGF23* mutations in ADHR result in impaired pro-teolysis of FGF23, resulting in increased serum levels of active FGF23. The disease shows incomplete penetrance, variable age at onset (childhood to adult), and resolution of the phosphate-wasting defect in rare cases. With treatment, prognosis is very good (Saito, Fukumoto, 2009; Orphanet-Autosomal Dominal...)

Autosomal Recessive Hyphosphatemic Rickets-1 (ARHR1)

(ICD-10 E83.3, Phenotype MIM number 241520, gene DMP1, locus 4q22.1) (OMIM entry 193100...).

ARHR is caused by inactivating mutations in dentin matrix acidic phosphoprotein (DMP1), a member of the SIBLING family of extracellular matrix protein that augments mineralization (18,33). Loss of DMP1 results in increased transcription of FGF23 by osteocytes), Dentin matrix protein 1 is noncollagenous extracellular protein, highly expressed in osteoblasts and osteocytes, in bone and teeth and belongs to a family of small integrinbinding ligand, N-linked glycoproteins (SIBLING) together with matrix proteins in calcified tissues such as dentin sialophosphoprotein (DSPP), integrin-binding sialoprotein (IBSP), matrix extracellular phosphoglycoprotein (MEPE), and osteopontin (Turan et al., 2010). Several homozygous mutations in *DMP1* gene were identified in patients with ARHR. However, it remains unclear how mutations in *DMP1* gene cause enhanced production of FGF23. Its phenotype profile includes Short stature; limited movement of spine and hip, calcification of the ligaments at the bony insertions sites, high bone density at the base of skull, clavicle and rib anomalies, enthesopathies and laboratory exams reveal how hypophosphatemia, low levels of serum 1,25-dihydroxyvitamin D, whereas serum calcium, parathyroid hormone, urinary calcium excretion are normal, and high circulating levels of FGF23 (OMIM entry 193100...; Turan et al., 2010, Masi et al., 2015).

Autosomal Recessive Hyphosphatemic Rickets-2 (ARHR2)

(ICD-10 E83.3, Phenotype MIM number 613312, gene ENPP1, locus 6q23.2)

Extremle rare disease that is caused by homozygous loss-of-function mutation in the ENPP1 gene; which encodes a protein called ectonucleotide pyrophosphatase/phosphodiesterase 1 (NPP1) (the latter is a major generator of extracellular pyrophosphate (PPi)). Because PPi inhibits calcification, inactivating mutations in ENPP1 gene are also responsible for generalized arterial calcification of infancy. In patients with ARHR2, high circulating levels of FGF23 have been described. FGF23 is a secreted protein, which reduces expression of sodium-phosphate co-transporters (NPT2a and NPT2c) resulting in renal phosphate wasting, diminishes the renal 1α-hydroxylase and increases the 24-hydroxylase activity. Moreover, FGF23 acts at the parathyroid gland to decrease parathyroid hormone synthesis and secretion. Currently, it is unclear how mutations in ENPP1 gene results in high FGF23 levels (Turan et al., 2010; Masi et al., 2015; OMIM entry...).

Hyperphosphatemic Familial Tumoral Calcinosis (HFTC)

(ICD-10 E83.3, Phenotype MIM number 613312, gene a) GALNT3-locus 2q24.2 b) FGF23-locus 12q13.32 c) KL-locus 13q13.1)

The disease causes hyperphosphatemia, hypercalcemia, elevated or inappropriately normal levels of 1,25 Vitamin D3 and ectopic calcifications which can be painful. GALNT3 mutations are the most often met. Yet, currently a Klotho gene mutation and 3 FGF23 gene mutations (Ser71Gly, Met96Thr, Ser129Phe) have been also described (Masi et al., 2015; ARHR2-International Osteoporosis Foundation...; OMIM entry 21190...; ADHR Consortium).

X-linked hypophosphatemic rickets (XLH)

(ICD-10 E83.3, Phenotype MIM number 307800, gene PHEX, locus Xq22.11)

It is the most common form of hereditary hypophosphatemia (prevalence of approximately 1/20,000, affects both sexes). PHEX encodes an endopeptidase expressed predominantly in bone and teeth that regulates fibroblast growth factor 23 (FGF-23) synthesis through unknown mechanisms. PHEX mutations lead to increased circulating levels of FGF-23, a phosphate-regulating hormone (phosphatonin), that leads to reduced renal phosphate reabsorption and consequently abnormal bone mineralization (Masi et al., 2015; Orpha89936-X-linked hypophosphatemia...).

XLH is caused by inactivating mutations of Phex (9), a cell surface endopeptidase that also is located in osteocytes. Loss of Phex also results in increased expression of FGF23 in osteocytes. The mechanism whereby loss of DMP1 and Phex upregulates FGF23 gene transcription is not known.

Single nucleotide Polymorphisms (SNPs) in FGF23 gene

A SNP in the intron of *FGF23* (c.212-37insC) is significantly associated with higher serum FGF23 levels and cardiac abnormalities in children with Kawasaki disease, while three distinct SNPs in *FGF23 gene* (rs11063118, rs13312789 and rs7955866) are associated with an increased risk of prostate cancer, indicating that *FGF23* genetic variations increase prostate cancer susceptibility (Itoh et al., 2015).

2. Renal disease

Chronic renal disease

Chronic kidney disease (CKD) is a growing public health epidemic that is associated with a markedly increased risk of cardiovascular mortality. Disordered mineral metabolism and particularly, disordered phosphorus metabolism appears to be a contributing factor (Wahl, Wolf, 2012). No correlation between FGF-23 and serum phosphate levels has been found in individuals without overt renal disease (Marsell et al., 2008). Yet, as CKD progresses and renal function declines FGF-23 levels gradually increase (up to 1000-fold above normal range in End Stage Renal Disease(ESRD)). Similar results were observed in studies that evaluated FGF23 in pediatric CKD population Even though FGF23 increase at a very early stage of CKD, there is no increase in the accumulation of degraded FGF-23 (C-terminals FGF23 or cFGF23) in advanced CKD. Possible explanations include physiological compensation to stabilize serum phosphate levels as the number of intact nephrons declines, the release of unidentified FGF-23 stimulatory factors or loss of a negative feedback factor(s) that normally suppress FGF-23 by the failing kidney or, an increased secretion due to an end-organ resistance to the phosphaturic stimulus of FGF-23 because of a deficiency of the necessary Klotho cofactor (Russo, Battaglia, 2011; Wolf, 2012). The mechanisms of how FGF23 is removed from the circulation, where and how it is degraded remain unknown. That is why clearance by the (failing) kidney or dialysis does not appear to contribute meaningfully to the circulating level (Wolf, 2012). On the contrary, FGF23 levels decline rapidly following kidney transplantation in most patients with prompt allograft function, however, persistently elevated FGF23 levels in the very early-post-transplant period contribute to post-transplant hypophosphatemia (Economidou et al., 2009).

Data from Chronic Renal Insufficiency Cohort (CRIC) study suggested that FGF23 is superior to existing markers as a sensitive screening test to identify which patients are developing disordered mineral metabolism in early CKD (Feldman et al., 2003). Several other studies identified FGF23 as a risk factor for CKD progression. Whether FGF23 is acting as a biomarker of cases of CKD that are destined to progress most rapidly or it is a direct mediator of disease progression is currently unknown (Economidou et al., 2009). Nevertheless, numerous reports

relate high FGF23 levels with progression to ESRD, cardiovascular disease, transfusion needs, infection susceptibility and death in CKD (Kendrick et al., 2011; Tsai et al., 2016).

As a result, several approaches (apart from surgical-kidney transplantation and parathyroidectomy) have been developed to lower FGF23 levels: dietary manipulation by reducing dietary phosphate intake; phosphate binders, especially non-calcium such as sevelamer, lanthanum, or aluminum-magnesium, cinacalcet, velcacetide and vitamin D (natural or analogues). Other modalities like e.g. anti-FGF23-Ab or RAAS blockade to modulation of the FGF23/Klotho/phosphate axis are also under evaluation (Wolf, 2012; de Seigneux, Martin, 2016).

Acute renal failure

Various reports reveal FGF23 role in acute renal failure (ARF) and acute kidney injury (AKI). Thus, cFGF23 levels rise early in AKI following cardiac surgery and are independently associated with adverse postoperative outcomes (Leaf et al., 2016). Among patients with AKI, FGF23 levels are elevated and associated with greater risk of death or need for renal replacement therapy (Leaf et al., 2012). Even though there was however no association between FGF23 levels and the severity of AKI, in some AKI models, FGF23 rised more quickly than phosphate levels or NGAL (Zhang et al., 2011; Christov et al., 2013). Recent study report that activation of FGFR1 is essential for the high levels of FGF23 in acute and chronic experimental uremia (Hassan et al., 2016). More studies are needed to identify the clear role of FGF23 in AKI.

3. Burns

Severe burn results in acute bone resorption followed by a dynamic state, most likely due to changes brought about by the inflammatory and glucocorticoid responses to the injury (Klein et al., 2015). Recent studies found increased FGF23 in adult burn patient, suggesting that osteocytes may be apoptotic (Klein et al., 2015; Rousseau, 2015). Moreover, an interesting correlation between CRP and FGF23 was found (Rousseau et al., 2014).

4. Stroke and Subarachnoid Hemorrhage (SAH)

In 2014 Northern Manhattan Study (NOMAS) found that elevated FGF23 was a risk factor for overall stroke and ICH events, in particular in a racially and ethnically diverse urban community, independent of chronic kidney disease (Wright, 2014). Later, the same investigators reported that carotid atherosclerosis may be a mechanism through which FGF23 increases cardiovascular events and stroke (Shah, 2015). Moreover, there is an association between elevated FGF23 and small vessel disease and magnetic resonance imaging-defined brain infarction in men, independent of chronic kidney disease (Wright et al., 2016). In Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, higher FGF23 concentrations were associated with higher risk of cardioembolic but not with other stroke subtypes in community-dwelling adults (Panwar, 2015). Finally, Söderholm and Engström report a relation of FGF23 with increased risk of incident SAH in subjects from the general population (Söderholm, Engström, 2015).

5. Neoplams

Phosphaturic mesenchymal tumor mixed connective tissue variants (PMTMCT)

PMTMCT is an extremely rare tumor of soft tissue which is typically associated with oncogenic osteomalacia (OO) or tumor induced osteomalacia (TIO). Classic histologic features of PMTMCT include osteoclast-like giant cells, spindle to stellate primitive mesenchymal cells, microcysts, and prominent vascularity, both blood vessels and lymphatics. FGF23 was identified as a causative humoral factor for TIO, which is quite rare in childhood FGF23 was shown to be abundantly expressed in tumors causing TIO Circulatory FGF23 levels are elevated in virtually all patients with TIO The surgical removal of responsible tumors results in normalization of FGF23 levels; while therapeutic approaches against FGF23 have also been used (Liao, 2013; Kinoshita, Fukumoto, 2014).

Prostate and ovarian cancer

As mentioned in Hereditary Diseases section, several studies relate SNPs of FGF23 or FGF23 levels with increased risk of prostate and ovarian cancer (Kim et al., 2014; Feng et al., 2013; Tebben et al., 2005).

6. Other

Results from a new study suggest that Increased serum FGF23 and placental growth factor (PLGF) levels and the presence of positive correlation between PLGF and Psoriasis area and severity index (PASI) score probably reflects the inflammatory state and insulin resistance seen in psoriasis (Okan et al., 2016).

Other investigators report that in mice model acute exercise, exhaustive exercise, and chronic exercise, increased serum FGF23 levels. Exercise-stimulated FGF23 promotes exercise performance via controlling the excess Reactive Oxygen Species production and enhancing mitochondrial function in skeletal muscle, which reveals an entirely novel role of FGF23 in skeletal muscle (Li et al., 2016).

Finally, in African Americans with type 2 diabetes lacking advanced nephropathy, FGF23 concentrations were independently associated with subclinical coronary artery disease (Freedman et al., 2015).

3. Conclusion

Along with its undoubted place in hereditary bone diseases and renal failure, in every stage, FGF23 role is far beyond clear. Further studies are needed to determine its place as prognostic, diagnostic or severity biomarker.

References

ADHR Consortium – ADHR Consortium. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nature Genet. 2000; 26: 345-348

Amin, 2014 – *Amin R.* (2014). Renal Klotho and mineral metabolism, Department of Clinical Science, Intervention and Technology, Division of Renal Medicine, Karolinska Institutet, Stockholm, Sweden 2014. Available from: https://openarchive.ki.se/xmlui/bitstream/handle/ 10616/41939/ Thesis_Risul_Amin.pdf?sequence=1

ARHR2-International Osteoporosis Foundation... – ARHR2-International Osteoporosis Foundation. Available from: http://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/skeletal-rare-disorders/autosomal-recessive-hypophosphatemi-0 (accessed 17/04/2016)

Christov et al., 2013 – *Christov M, Waikar SS, Pereira RC, Havasi A, Leaf DE, Goltzman D, Pajevic PD, Wolf M, Jüppner H. Plasma* (2013). FGF23 levels increase rapidly after acute kidney injury. *Kidney Int*. 84(4): 776-785.

de Seigneux, Martin, 2016 – *de Seigneux S, Martin PY.* (2016). Phosphate and FGF23 in the renoprotective benefit of RAAS inhibition. *Pharmacol Res*. 106: 87-91.

Economidou et al., 2009 – *Economidou D, Dovas S, Papagianni A*, Pateinakis P, Memmos D. (2009). FGF-23 levels before and after renal transplantation. *J Transplant*. 379082.

Feldman et al., 2003 – Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, Fink JC, Franklin-Becker ED, Go AS, Hamm LL, He J, Hostetter T, Hsu CY, Jamerson K, Joffe M, Kusek JW, Landis JR, Lash JP, Miller ER, Mohler ER, III, Muntner P, Ojo AO, Rahman M, Townsend RR, Wright JT. (2003). The Chronic Renal Insufficiency Cohort (CRIC) Study: design and methods. *J Am Soc Nephrol*. 14: P. 148–153.

Feng et al., 2013 – *Feng S, Dakhova O, Creighton CJ, Ittmann M.* (2013). Endocrine fibroblast growth factor FGF19 promotes prostate cancer progression. Cancer Res. 73(8): 2551-2562.

Finklestein, Plomaritoglou, 2001 – *Finklestein S.P., Plomaritoglou A.* (2001). Growth factors. In Miller L.P., Hayes R.L., eds. Co-edited by Newcomb J.K. Head Trauma: Basic, Preclinical, and Clinical Directions. New York: Wiley, pp. 165–187.

Freedman et al., 2015 – *Freedman BI, Divers J, Russell GB, Palmer ND, Bowden DW, Carr JJ, Wagenknecht LE, Hightower RC, Xu J, Smith SC, Langefeld CD, Hruska KA, Register TC.* (2015). Plasma FGF23 and Calcified Atherosclerotic Plaque in African Americans with Type 2 Diabetes Mellitus. *Am J Nephrol*. 42(6): 391-401.

Hassan et al., 2016 – *Hassan A, Durlacher K, Silver J, Naveh-Many T, Levi R.* (2016). The fibroblast growth factor receptor mediates the increased FGF23 expression in acute and chronic uremia. *Am J Physiol Renal Physiol*. 310(3): F. 217-21.

Itoh et al., 2015 – *Itoh N, Ohta H, Konishi M.* (2015). Endocrine FGFs: physiology, evolution, pathophysiology and pharmacotherapy. *Front Endocrinol (Lausanne)*. 29(6): 154.

Itoh, Ornitz, 2004 – *Itoh N, Ornitz DM* (2004). Evolution of the Fgf and Fgfr gene families. *Trends Genet*. 20: 563–569.

Itoh, Ornitz, 2008 - *Itoh N, Ornitz DM*. (2008). Functional evolutionary history of the mouse Fgf gene family. *Developmental Dynamics*. 237 (1): 18–27.

Kendrick et al., 2011 – *Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, Chonchol M* (2011). HOST Investigators. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol*. 22(10): 1913-1922

Kim et al., 2014 – *Kim HJ, Kim KH, Lee J, Oh JJ, Cheong HS, Wong EL, Yang BS, Byun SS, Myung SC*. (2014). Single nucleotide polymorphisms in fibroblast growth factor 23 gene, FGF23, are associated with prostate cancer risk. *BJU Int*. 114(2): 303-310.

Kinoshita, Fukumoto, 2014 – *Kinoshita Y, Fukumoto S*. (2014). Anti-FGF23 antibody therapy for patients with tumor-induced osteomalacia. *Clin Calcium*. 24(8): 1217-1222.

Klein et al., 2015 – *Klein GL, Herndon DN, Le PT, Andersen CR, Benjamin D, Rosen CJ*. (2015). The effect of burn on serum concentrations of sclerostin and FGF23. *Burns*. 41(7): 1532-1335.

Leaf et al., 2012 – *Leaf DE, Wolf M, Waikar SS, Chase H, Christov M, Cremers S, Stern L*. (2012). FGF-23 levels in patients with AKI and risk of adverse outcomes. Clin J Am Soc Nephrol. 7(8):1217-1223.

Leaf et al., 2016 – *Leaf DE, Christov M, Jüppner H, Siew E, Ikizler TA, Bian A, Chen G, Sabbisetti VS, Bonventre JV, Cai X, Wolf M, Waikar SS*. (2016). Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery. *Kidney Int*. 89(4): 939-48.

Li et al., 2016 – *Li DJ, Fu H, Zhao T, Ni M, Shen FM*. (2016). Exercise-stimulated FGF23 promotes exercise performance via controlling the excess reactive oxygen species production and enhancing mitochondrial function in skeletal muscle. *Metabolism*. 65(5): 747-756.

Liao, 2013 – *Liao E*. (2013). FGF23 associated bone diseases. Front Med. 7(1): 65-80.

Liu et al., 2003 – *Liu S, Guo R, Simpson LG, Xiao ZS, Burnham CE, Quarles LD*. (2003). Regulation of fibroblast growth factor 23 expression but not degradation by PHEX. *J Biol Chem*. 278: 37419-26.

Liu, Quarles, 2007 – *Liu S, Quarles LD*. (2007). How fibroblast growth factor 23 works. J Am Soc Nephrol 2007; 18:1637-47.

Marsell et al., 2008 – *Marsell R, Grundberg E, Krajisnik T, Mallmin H, Karlsson M, Mellström D et al*. (2008). Fibroblast growth factor-23 is associated with parathyroid hormone and renal function in a population-based cohort of elderly men. *European Journal of Endocrinology*. 158(1):125-129

Masi et al., 2015 – *Masi L, Agnusdei D, Bilezikian J, Chappard D, Chapurlat R, Cianferotti L, Devolgelaer JP, El Maghraoui A, Ferrari S, Javaid MK, Kaufman JM, Liberman UA, Lyritis G, Miller P, Napoli N, Roldan E, Papapoulos S, Watts NB, Brandi ML*. (2015). Taxonomy of rare genetic metabolic bone disorders. Osteoporos Int. 2015; 26(10): 2529-2558.

Okan et al., 2016 – *Okan G, Baki AM, Yorulmaz E, Doğru-Abbasoğlu S, Vural P*. (2016). Fibroblast Growth Factor 23 and Placental Growth Factor in Patients with Psoriasis and their Relation to Disease Severity. *Ann Clin Lab Sci*. 46(2): 174-179.

Olsen et al., 2003 – *Olsen SK, Garbi M, Zampieri N, Eliseenkova AV, Ornitz DM, Goldfarb M, Mohammadi M*. (2003). Fibroblast growth factor (FGF) homologous factors share structural but not functional homology with FGFs. *The Journal of Biological Chemistry*. 278 (36): 34226–36.

OMIM entry 193100... – OMIM entry 193100-Hyphosphatemic rickets, autosomal dominant. Available from: http://www.omim.org/entry/193100 (accessed 14/04/2016)

OMIM entry 193100... – OMIM entry 193100-Hyphosphatemic rickets, autosomal recessive 1. Available from: http://www.omim.org/entry/241520 (accessed 15/04/2016)

OMIM entry 21190... – OMIM entry 21190-Tumoral calcinosis, familial. Available from: http://www.omim.org/entry/211900 (accessed 18/04/2016)

OMIM entry... – OMIM entry 613312 Hyphosphatemic rickets, autosomal recessive 2. Available from: http://www.omim.org/entry/613312 (accessed 15/04/2016)

Ornitz, 2000 – *Ornitz DM* (2000). FGFs, heparan sulfate and FGFRs: Complex interactions essential for development. Bioessays 2000; 22: 108–112.

Orpha89936-X-linked hypophosphatemia... – Orpha89936-X-linked hypophosphatemia – Orhpanet. Available from: http://www.orpha.net/consor/cgibin/Disease_Search.php?lng=

EN&data_id=11911&Disease_Disease_Search_diseaseGroup=307800&Disease_Disease_Search_diseaseType=OMIM&Disease%28s%29/group%20of%20diseases=X-linked- hypophosphatemia &title=X-linked (accessed 20/04/2016)

Orphanet-Autosomal Dominal... – Orphanet-Autosomal Dominal Hypophosphatemic Rickets. Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=89937 (accessed 15/4/2016)

Panwar, 2015 – *Panwar B, Jenny NS, Howard VJ, Wadley VG, Muntner P, Kissela BM, Judd SE, Gutiérrez OM.* (2015). Fibroblast growth factor 23 and risk of incident stroke in community-living adults. Stroke. 46(2): 322-328.

Rossaint et al., 2016 – *Rossaint J, Oehmichen J, Van Aken H, Reuter S, Pavenstädt HJ, Meersch M, Unruh M, Zarbock A.* (2016). FGF23 signaling impairs neutrophil recruitment and host defense during CKD. J Clin Invest. 2016;126(3):962-974

Rousseau et al., 2014 – *Rousseau AF, Damas P, Ledoux D, Cavalier E.* (2014). Effect of cholecalciferol recommended daily allowances on vitamin D status and fibroblast growth factor-23: an observational study in acute burn patients. *Burns*. 40(5): 865-870.

Rousseau, 2015 – *Rousseau AF, Damas P, Ledoux D, Lukas P, Carlisi A, Le Goff C, Gadisseur R, Cavalier E.* (2015). Vitamin D status after a high dose of cholecalciferol in healthy and burn subjects. Burns. 41(5): 1028-1034.

Russo, Battaglia, 2011 – *Russo D., Battaglia Y.* (2011). Clinical signigicance of FGF23 in patients with CKD. *Int J Nephr*. Article ID 364890

Saito, Fukumoto, 2009 – *Saito T, Fukumoto S.* (2009). Fibroblast growth factor 23 and disorders of phosphate metabolism. *Int J Ped Endicronology*, Article ID 496514, doi: 10.1155/2009/496514

Schnedl et al., 2015 – *Schnedl C, Fahrleitner-Pammer A, Pietschmann P, Amrein K.* (2015). FGF23 in Acute and Chronic illness. *Dis Markers*. 358086.

Shah, 2015 – *Shah NH, Dong C, Elkind MS, Sacco RL, Mendez AJ, Hudson BI, Silverberg S, Wolf M, Rundek T, Wright CB.* (2015). Fibroblast Growth Factor 23 Is Associated With Carotid Plaque Presence and Area: The Northern Manhattan Study. Arterioscler Thromb Vasc Biol. 35(9): 2048-2053.

Shimada et al., 2004 – *Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T (2004).* Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest*. 113: 561–568.

Söderholm, Engström, 2015 – *Söderholm M, Engström G* (2015). Fibroblast Growth Factor 23 and Incidence of Subarachnoid Hemorrhage: Nested Case-Control Study. *Stroke*. 46(11): 3260-3262.

Tebben et al., 2005 – *Tebben PJ, Kalli KR, Cliby WA, Hartmann LC, Grande JP, Singh RJ, Kumar R.* (2005). Elevated fibroblast growth factor 23 in women with malignant ovarian tumors. *Mayo Clin Proc*. 80(6): 745-751.

Tsai et al., 2016 – *Tsai MH, Leu JG, Fang YW, Liou HH.* (2016). High Fibroblast Growth Factor 23 Levels Associated With Low Hemoglobin Levels in Patients With Chronic Kidney Disease Stages 3 and 4. *Medicine (Baltimore)*. 95(11): 3049.

Turan et al., 2010 - *Turan S, Aydin C, Bereket A, Ackay T, Guran T, Yaralioglou BA, Basteppe M, Murat H.* (2010). Identification of a novel dentin matrix protein-1 (DMP-1) mutation and dental anomalies in a kindred with autosomal recessive hypophosphatemia. *Bone*. 46(2): 402-409.

Urakawa, 2006 – *Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T.* (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 444: 770–774.

Wahl, Wolf, 2012 – *Wahl P, Wolf M.* (2012). FGF23 in chronic renal disease. *Adv Exp Med Biol*. 728: 107-125.

Wolf, 2012 – *Wolf M.* (2012). Update on Fibroblast growth factor 23 in chronic kidney disease. *Kidney Int*. 82(7): 737-747

Wright et al., 2016 – Wright CB, Shah NH, Mendez AJ, DeRosa JT, Yoshita M, Elkind MS, Sacco RL, DeCarli C, Rundek T, Silverberg S, Dong C, Wolf M. Fibroblast Growth Factor 23 Is Associated With Subclinical Cerebrovascular Damage: The Northern Manhattan Study. Stroke. 47(4):923-928.

Wright, 2014 – *Wright CB, Dong C, Stark M, Silverberg S, Rundek T, Elkind MS, Sacco RL, Mendez A, Wolf M*. (2014). Plasma FGF23 and the risk of stroke: the Northern Manhattan Study (NOMAS). Neurology. 82(19): 1700-1706.

Yamashita et al., 2000 – *Yamashita T, Yoshioka M, Itoh N*. (2000). Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. Biochem Biophys Res Commun 2000; 277: 494–498.

Yu et al., 2005 – *Yu X, Ibrahimi OA, Goetz R, Zhang F, Davis SI, Garringer HJ, Linhardt RJ, Ornitz DM, Mohammadi M, White KE* (2005). Analysis of the biochemical mechanisms for the endocrine actions of fibroblast growth factor-23. Endocrinology 146: 4647–4656.

Zhang et al., 2011 – *Zhang M, Hsu R, Hsu CY, Kordesch K, Nicasio E, Cortez A, McAlpine I, Brady S, Zhuo H, Kangelaris KN, Stein J, Calfee CS, Liu KD*. (2011). FGF-23 and PTH levels in patients with acute kidney injury: A cross-sectional case series study. *Ann Intensive Care*. 4;1(1): 21.

Published in the Russian Federation
European Journal of Medicine
Has been issued since 2013.
ISSN: 2308-6513
E-ISSN: 2310-3434
Vol. 14, Is. 4, pp. 100-109, 2016

DOI: 10.13187/ejm.2016.14.100
www.ejournal5.com

The Efficacy of Primary Surgery Compared to Post Chemotherapy Surgery for Patients with Locally Advanced Breast Cancer

Ibrahim Albalawi [a, *]

[a] Department of Surgery, Faculty of Medicine, University of Tabuk, Saudi Arabia

Abstract

Purpose: to compare primary surgery and surgery after neoadjuvant chemotherapy (NCT) in locally advanced breast cancer (LABC) patients for whom loco-regional& systemic treatment in the form of chemotherapy and radiotherapy were performed. Patients and methods: Between 2008 & 2011, 112 patients with LABC were treated at KAAH & OC-Jeddah-KSA. Of whom 42 were treated by NCT followed by surgery either mastectomy or conservative surgery, then adjuvant chemotherapy and radiotherapy. The rest patients (70) were treated by primary surgery (mastectomy or conservative resection) followed by adjuvant chemotherapy and radiotherapy. All patients received adjuvant antiestrogen. Patients were followed for a median duration of 33 months. Disease- free survival (DFS) and overall survival (OAS) were studied for all patients, compared between both groups and related to extent of surgery and menopausal status.

Results: median age was 46.5 years for all patients. 48 years, and 46 years for NCT and primary surgery groups respectively. Median DFS was 15 months for all patients, 16 & 15 months for NCT and primary surgery groups. Median OAS was 24 months for all patients, 22 & 24 months for NCT and primary surgery groups. Difference in DFS& OAS were highly significant in favor of postmenopausal patients ($p = 0.05$ for DFS & $p = 0.03$ for OAS) while in primary surgery group the differences between pre and postmenopausal patients in DFS & OAS were statistically insignificant ($p = 0.4$). NCT followed by surgery group patients showed significant improvement in DFS & OAS in patients performed conservative surgery while in primary surgery group the difference was insignificant. The results of neoadjuvant chemotherapy showed (14.3%) complete clinical remission (33.3%) showed more than 50% primary tumor regression, while the rest of patients (52.4%) showed less than 50% reduction of the primary tumor. The incidence of metastases was 56.5% for all patients, 49.4% for NCT group and 61.1% for primary surgery group. Freedom of disease was seen in 28.6% in NCT group and 37.1% for primary surgery group and local recurrence was noticed in 23.8% in NCT group Vs 2.9% in the primary surgery group.

Conclusion: Surgery post-neoadjuvant chemotherapy neither prolongs DFS nor OAS in comparison with primary surgery followed by adjuvant chemotherapy. However, it permits more conservative surgery to be performed in LABC patients, but many of these patients could not achieve complete pathological remission leading to increased incidence of local failure. Postmenopausal patients fared much better than premenopausal patients regarding DFS & OAS. Earlier surgical interference with modified radical mastectomy for those who showed minimal response to NCT (after 2 courses) is highly recommended. Alternatively, aggressive treatment with

* Corresponding author
E-mail addresses: drbalawi@yahoo.com (I. Albalawi)

newer chemotherapeutic drugs or increasing dose intensity plus growth factor support may be warranted for younger patients to improve the outcome of conservative surgery.

Keywords: primary surgery, neoadjuvant chemotherapy, locally advanced breast cancer, mastectomy and conservative surgery.

1. Introduction

Locally advanced breast carcinoma (LABC) comprises a heterogeneous group of tumors ranging from relatively large primary tumors (stage T4) to small breast tumors presenting with extensive nodal metastases (involvement of ipsilateral, infraclavicular, supraclavicular, or internal mammary nodes). It remains a clinical challenge as the majority of patients with this diagnosis develop distant metastases despite appropriate therapy (Singletary et al., 2002), inflammatory carcinomas also included in locally advanced breast carcinoma (Cristofanilli et al., 2003). It is defined by 1992 American Joint Committee (AJC) staging criteria as stage IIIa and IIIb disease (Taylor et al., 1997). Despite the awareness of physician and public of the importance of screening and early detection, 10-20% of women with breast cancer have locally advanced disease at diagnosis in industrialized countries (14% in the United States) while in developing countries it might constitute up to 50% of incident cases (Hortobagyi et al., 1995). In populations that receive regular screening mammography, the percentage of patients with the locally advanced disease is less than 5% (Seidman et al., 1987). The treatment for patients with locally advanced breast cancer is typically a combination of systemic chemotherapy, surgery, and radiotherapy. There is a consensus that all patients with the technically resectable disease should have radical mastectomy (Taylor et al., 1997). Earlier results of radical mastectomy alone were associated with a 53% local failure rate and a zero % 5-year disease free survival (Harris et al., 1992). Similarly radiation therapy alone for these patients resulted in poor 3-year survival (10–25%) with significant risk for disease recurrence and death, as well as the complications of soft tissue, ribs, heart and lung injury, also brachial plexopathy, lymphedema, chest wall fibrosis, skin ulceration, and skin necrosis (Harris et al., 1992). The combination of surgery and radiotherapy although decrease incidence of local failure, a high frequency of distant metastasis were seen after either treatment approaches. The introduction of multimodality treatment with the addition of chemotherapy has resulted in improvement of disease-free survival particularly in stage IIIA (Taylor et al., 1997, Harris et al., 1992).

Neoadjuvant chemotherapy (NCT) was developed in 1970 and is used before local treatment in LABC to downstage the primary tumor to make subsequent surgery easier, hoping to eliminate occult distant metastasis to prolong survival (Wang et al., 1996). The natural history of this disease has been changed dramatically by the introduction of these combined modality therapies with 5-year survival rate of 35–60% commonly are reported (Hortobagyi et al., 1995). Despite the theoretical and experimental data indicating the survival superiority of neoadjuvant chemotherapy over postoperative adjuvant chemotherapy, the role of neoadjuvant in staging remains unclear (Wang et al., 1996), and there are few studies that compare this approach to postoperative treatment (Taylor et al., 1997, Cuningham et al., 1998). The purpose of this study is to compare the disease-free survival (DFS) and overall survival (OAS) of patients with LABC treated with NCT, surgery and radiotherapy to patients treated by primary surgery followed by adjuvant chemotherapy and radiotherapy and to study the prognostic impact of menopausal status and extent of surgical resection on these survival parameters.

2. Material and Methods

Eligible patients for this study are those with technically resectable non-inflammatory locally advanced cancer breast (stage III A & B). 112 patients with previous criteria were treated at King Abdul Aziz Hospital and Oncology Center-Jeddah-Kingdom of Saudi Arabia between May 1998 and April 2002 and between June 2007 and May 2011. These patients were treated by multimodality therapy and have been classified into two groups according to whether they were initially treated by neoadjuvant chemotherapy or by surgery. The first group (NCT) included 42 patients who were primarily treated with neoadjuvant chemotherapy followed by surgery after biopsy proven carcinoma and staging work-up at the oncology center. Those patients received FAC regimen (5 flurouracil, doxorubicin and cyclophosphamide), then followed by surgery in the form modified radical mastectomy or conservative resection and axillary clearance. All patients received postoperative radiotherapy to chest wall or breast and lymphatic drainage site. Adjuvant hormone

therapy (antiestrogen) was given to all patients regardless of the hormone receptor status plus adjuvant 4 courses of chemotherapy (postoperatively). The second group (Primary surgery) included 70 patients who were referred to the oncology center for adjuvant postoperative management. Those patients have been staged and defined as locally advanced cancer breast (IIIA & IIIB) by surgical and pathology teams. Patients were operated either by modified radical mastectomy or by conservative surgery and axillary clearance. Those patients have been staged and defined as locally advanced cancer breast (IIIA & IIIB) by surgical and pathology teams. Patients were operated either by modified radical mastectomy or by conservative surgery and axillary clearance. For those patients staging work up was performed, including full blood picture, biochemical profile, chest X-ray (CXR), abdominal ultrasonography, bone scan and study of left ventricular ejection fraction by MUGA scan (the later performed for patients who were planned to receive anthracycline).

These second group patients were treated by triple modality i.e. surgery followed by adjuvant chemotherapy (6 courses of CMF or FAC) followed by postoperative radiotherapy to chest wall or breast and peripheral lymphatic. All patients received hormone therapy (antiestrogen) regardless of the hormone receptor status.

Main outcome measures

All the patients have been followed up regularly for either recurrence, disease-free interval or death, this continued for two years minimum and five years maximum (median 33 months) Check up in the form of CXR, abdominal ultrasound six monthly and bone scan yearly or whenever clinically indicated. Comparative analysis of the two groups regarding disease-free survival (DFS) and overall survival (OAS) was done. The incidence of disease progression as well as the type of progression was studied for all patients and for both groups separately with statistical evaluation of the results. The prognostic significance of extent of surgery and menopausal status were studied and correlated to DFS, OAS and disease progression with statistical evaluation of the results in both groups.

The chemotherapy: consist of FAC regimen (5-Fu 500 mg/m2/D1 cyclophosphamide 500 mg/m2/D1 doxorubicin 50 mg/m2/D1. This course was repeated every three weeks. (Patients with ejection fraction less than 50%, doxorubicin was replaced by mitoxantrone 12 mg/m2). The hormonal treatment was Anti-estrogen (Tamoxifen) 20 mg/day orally was prescribed for all patients and continued all over treatment period and is planned to be taken for 5 years. The postoperative irradiation used for the treatment of all patients by the linear accelerator to a dose of 5040 cGy/28 fractions for chest wall with an electron beam and peripheral lymphatics (with photon beam). Patients with intact breast received their treatment with the above-mentioned dose with photon beam and the primary site was boosted to 6000–6500 cGy total dose with an electron beam.

Statistical evaluation: Fisher's exact test was used for comparative statistical significance.

3. Results

The median age for the whole group was 46.5 years and the mean age was 46.19±14.69 years (range 23-75) and the peak age was in the third forth decade which represents 50% of all patients (Table 1). No difference was noticed in the median age between neoadjuvant chemotherapy group (NCT) and surgery or adjuvant group (surgery) 48 and 46 years respectively (Table 2)

Premenopausal patients constitute 62.5% of whole patients while 37.5% were postmenopausal. In both studied groups (NCT) and (surgery) 57% and 56% were premenopausal while 43% and 35% were postmenopausal respectively (Table 2). Analysis of survival parameters revealed that the median disease-free survival (DFS) for all patients was 15 months and the median overall survival (OAS) was 24 months and there was no difference in (DFC) in (NCT followed by surgery) group and the primary surgery group (16 months and 15 months) as well as the OAS (22 months and 24 months in NCT and the primary surgery group respectively (Tables 3, 4). The influence of menopausal status revealed a highly significant improved differences in DFS and OAS for postmenopause versus premenopause for all patients with DFS 12 months for menopause versus 24 menopause (p=0.01). Similarly, OAS was 18 months in premenopause versus 27 months for postmenopause (p=0.01) (Table 3).

These differences were also noted in NCT followed by surgery group where DFS was 10.5 months for pre menopause and 29 months for post menopause with (p=0.05) and OAS was 15.5 months and 35 months for pre and post menopause respectively (p=0.03). In the primary surgery group this difference in DFS and OAS for pre and post menopause was statistically insignificant (p=0.04) (Table 4). Although the noticed improvement of DFS in NCT followed by surgery group versus the primary surgery group in postmenopausal patients (median 29 months versus 19.5 months), but the difference was statistically insignificant (p=0.06). Similarly, the OAS was 35 months in NCT group versus 24 months in the primary surgery group in postmenopausal patients and also the difference was statistically insignificant (p=0.5) (Table 4). Relating the survival data to the extent of surgery performed revealed that the median DFS was 12 months for patients performed modified radical mastectomy (MRM) and 20 months for those patients performed conservative surgery, but the difference was statistically insignificant (p=0.03). Similarly, the OAS was 24 and 29 months for those performed MRM and conservative surgery respectively with statistically insignificant difference between both groups (p=0.06). However, when survival parameters and extent of surgery were studied within each treatment group, it revealed a statistically insignificant difference in the surgery group for DFS (p=0.8) and OAS (p=0.7) for those performing MRM and conservative surgery (Table 5). But in the NCT followed by surgery group, there was statistically significant difference for DFS (P=0.02) and OAS (p=0.02) in favor of patients performing conservative surgery. It was also noted in patients performed MRM that there was a statistically significant difference in favor of the primary surgery group versus NCT followed by surgery group regarding DFS (15 Vs. 8 months, p=0.02) and OAS (24 Vs 15.5 months, p=0.02) (Table 5). The effect of primary chemotherapy in (NCT followed by surgery) group revealed that 6 patients (14.3%) showed complete clinical remission, 14 patients (33.3%) showed more than 50% regression of the primary tumor while 22 patients (52.4%) showed less than 50% regression of the primary tumor. There was no pathological complete remission among patients who achieved complete clinical remission, however, pathologically free margin was achieved for all patients performed post chemotherapy conservative excision.

Regarding treatment results, the incidence of metastatic disease was 55.4% for all patients, 47.6% in NCT followed by surgery group and 60% in the primary surgery group with statistically borderline significant difference between both groups (p=0.07). Freedom of disease was achieved in 33.9% of all patients, 28.6% for NCT followed by surgery group and 37.1% for the primary surgery group with statistically borderline significant difference between both groups (p=0.08). As for local recurrence, only 2/70 of patients in the primary-surgery group (2.9%) experienced local recurrence versus 10/42 patients (23.8%) in NCT followed by surgery group. Statistical analysis could not be estimated for this category due to the presence of only two patients in the primary-surgery group (Table 6).

Table 1. Age group distribution in locally advanced cancer breast

	Age groups	No.	%
1	20 -< 30	12	10.7
2	30 -< 40	28	25
3	40 -< 50	30	26.8
4	50 -< 60	14	12.5
5	60 -< 70	14	12.5
6	> 70	16	14.3
Total		112	100

Table 2. Patients characteristic in both groups

Patients characteristic	Neoadjuvant followed by surgery	Primary surgery
Number	42	70
Age (median)	48	46
Menopause:		
Premenop-	24	46
Postmenop	18	70
Tumour status:		
T2		12
T3	30	34
T4	12	20
Tx		4
Nodal status:		
N1	36	38
N2	6	24
Nx		8
Surgical procedures:		
Mod. Rad. Mas.	20	62
Conservative surgery	22	8

Table 3. Survival parameters in correlation with menopausal status

	No.	Dis. Free survival (median)	Overall survival (median)
Premenopause	70	12*	18**
Postmenopause	42	24*	27**
Total	112	15	24

**p=0.01*
***p=0.01*

Table 4. survival parameters (median values) in correlation to menopausal status in both studied groups

	Neoadjuvant group			Surgery group		
	No.	DFS	OAS	No	DFS	OAS
Premenopausal	24	10.5*	15.5[a]	46	12[1]	20[2]

Postmenopausal	18	[b]29*	35[a]	24	[b]19.5[1]	24[2]
Total		16	22	35	15	24

*p=0.05 [2]p=0.4 [a]p=0.03[b]p=0.6[1]p=0.4[c]p=0.5

Table 5. Survival parameters (median values) in correlation to the extent of surgery in the studied groups

	All patients			Neoadjuvant followed by surgery group			Primary surgery group		
	No.	DFS	OAS	No.	DFS	OAS	No.	DFS	OAS
Modified radical mastectomy	82	12	24	20	[1]8[a]	[b]15.5[2]	62	[3]15[a]	[b]24+
Conservative surgery + axillary clearance	30	20	29	22	[1]16	35[2]	8	[3]15	19+
Total	56	15	24	21	16	22	35	15	24

[a]p=0.02 [b]p=0.02 [1]p=0.02 [3]p=0.8 [+]p=0.7

Table 6. Results of treatment in correlation to the treatment strategy adopted for locally advanced cancer breast

Patient status	All patients		Neoadjuvant group		Surgery group	
	No.	%	No.	%	No.	%
Free	38	33.9	12	28.6*	26	37.1*
Local recurrence.	12	10.7	10	23.8	2	2.9
Metast. Dis.	62	55.4	20	47.6**	42	60**
Total	56	100	21	100	35	100

*p=0.08 **p=0.07

3. Discussion

Locally advanced breast carcinoma is associated with a poor prognosis; with single treatment modality, i.e. surgery, and/or radiotherapy, results has been consistently dismal (Karlesson et al., 1998). The appropriate management of locally advanced breast cancer is controversial, the trends towards a more effective means of improving response rates and survival have shifted to earlier aggressive treatment and the strength in the management of LABC lies in the team approach to multimodality care (Singletary et al., 1995). The sequence of treatment in those patients still has to be optimized since despite the theoretical and experimental data indicating the survival superiority of neoadjuvant followed by surgery over primary surgery with adjuvant chemotherapy. The role of neoadjuvant chemotherapy in the treatment of breast cancer remains unclear although downstaging of the primary tumor is confirmed (Wang et al., 1996). In the present study which

aimed at comparison of patients treated with neoadjuvant chemotherapy followed by surgery and those treated by primary surgery followed by adjuvant chemotherapy, analysis of data revealed that the median age was 46.5 years and the mean was 47.19±14.69 years. This median age was also reported from a similar study performed in KFSH-Riyadh study (Ibrahim et al., 1999). This mean age is not different from the overall age incidence for breast cancer in Saudi Arabia, which reported mean age at diagnosis to be 48.3 years (Cancer Incidence SA, 1999). Premenopausal patients comprise 62.5% of all patients and 37.5% postmenopausal, this incidence was similar to that reported by KFSH-Riyadh (Ibrahim et al., 1999).

Analysis of survival data revealed that the median DFS in our patients was 16 months, a similar figure (17 months) was reported in a similar study (Eisten et al., 1998). No difference in DFS and OAS was noticed in patients treated by NCT followed by surgery or by primary surgery, this finding has been documented by Fisher (Fisher et al., 1998), who compared preoperative with postoperative therapy in operable breast cancer patients including LABC cases and found no difference in DFS and OAS between pre and postoperative chemotherapy. Cunningham (Cuningham et al., 1998) and Kuerer (Kuerer et al., 1999) also found so significant difference in DFS and OAS between NCT and postoperative adjuvant treatment.

This significance of menopausal status in this study showed that DFS and OAS were significantly better in older age group (postmenopause). This finding has been studied by Crowe (Crow et al., 1994) who found that younger patients had more estrogen receptor negative tumors and a greater number of positive lymph nodes and he concluded that younger patients as a group has more aggressive and advanced cancer compared to older patients, but it should not be used alone for management decision. This was reported also by Newman (Newman et al., 1998) who confirmed that younger women tend to present with more locally advanced breast cancer and their tumors may have different response to treatment, compared to older patients and hence this significant difference in survival is a reflection of the aggressive nature of the disease in younger age group.

The second finding concerning age in our results was noticed by inspecting the insignificant difference in DFS and OAS for pre and postmenopausal patients in the primary surgery group and also postmenopausal patients in either group. This finding could suggest the possibility that younger age group might benefit from earlier surgical interference in premenopausal patients especially those who initially showed minimal response to chemotherapy (after 2 courses). Although, the DFS and OAS were more or less similar in both groups; however earlier surgery for premenopausal patients may abolish this significant difference in survival between pre and post menopause for patients treated with neoadjuvant chemotherapy.

Considering the extent of the surgery, the insignificant difference in survival parameters (DFS and OAS) for all patients and also for patients in primary surgery group could be explained by the fact that the main problem in patients with LABC is the distant failure regardless the locoregional control of the disease (Taylor et al., 1997; Harris et al., 1997). For this reason, recent trials and utilizing aggressive chemotherapy with newer agents like Texas (Philiph et al., 2000; Esteva et al., 2000) or by increasing dose intensity in conjunction with growth factors to increase the response of the tumors to primary chemotherapy which may improve the survival and this is reported in southwest oncology group phase II trials (Ellis et al., 2000).

On the other hand, in NCT followed by surgery group, there was the discrepancy in the results since there was the significant difference in survival parameters (DFS and OAS) favoring patients who performed conservative surgery. However, this finding could be explained by the fact that patients who performed conservative surgery were those who showed excellent response to primary chemotherapy and they achieved better results than those who showed minimal response to chemotherapy and consequently performed modified radical mastectomy did. These results were also reported by Schwartz (Schwartz et al., 1994) who showed in their series of patients treated by neoadjuvant chemotherapy a five-year disease-free survival 56% for those having mastectomy and 77% for those having breast conservation and five years overall survival was 67% for those performed mastectomy and 80% for those having breast conservation. Resent trials currently are using aggressive chemotherapy to achieve a higher remission clinically and pathologically in order to improve DFS and OAS (Philiph et al., 2000; Esteva et al., 2000; llis et al., 2000). Worth mentioning that those responsive patients to primary chemotherapy who underwent conservative surgery might

be responsive also to the adjuvant chemotherapy postoperatively and that is why they showed improved survival parameters in comparison with all other subsets of patients.

Regarding treatment results, freedom of disease was noticed in 37.1% of primary surgery group Vs 28.6% in NCT followed by surgery group with the borderline significant (p=0.08). This could be explained by the presence of only one patient with local recurrence in the primary surgery group Vs 5 in the NCT followed by surgery group and this is the consequence of a large number of patients performed conservative surgery in the NCT group (22 patients) versus only eight patients in the primary surgery group. This finding was reported by Taylor (Taylor et al., 1997) who found that mastectomy substantially decreased locoregional recurrence but distant metastases were a major component of failure. This was noticed in this work, where there is 60% incidence of metastatic disease in the primary surgery group Vs 47.6% in NCT followed by surgery group with the borderline significant difference (p=0.07). This could be explained by the fact that most LABC patients would be already harbouringmicrometastases at their initial diagnosis, that should be primarily treated by chemotherapy as it was suggested that chemotherapy may modulate the host environment to prevent tumor cell migration (Murthy et al., 1999).

4. Conclusion

The results of this study showed that primary surgery followed by postoperative therapy is comparable to neoadjuvant therapy followed by surgery in LABC regarding disease-free survival, overall survival, distant failure and disease control. However, local recurrence was higher in NCT followed by surgery group because of the favorability of conservative resection in both patients and surgeons side once they got tumor shrinkage, but we have to give attention to what was reported about this situation by Kent (Kent et al., 1995) who found that chemotherapy is useful in reducing tumor size to allow surgical resection but does not sterilize the breast of cancer and they caution against the use of any surgery less than total mastectomy in partially responsive tumor if optimal local control is to be achieved in locally advanced breast cancer. Secondly, the post menopause (older age) patients fared much better than younger age regarding survival parameters particularly with NCT followed by surgery group. So, we recommend that younger patients who deserve neoadjuvant chemotherapy have to be treated aggressively by surgery not less than mastectomy. The other alternative is the use of a newer chemotherapeutic agents or increasing dose intensity of chemotherapy to obtain a higher clinical and pathological remission so that conservative surgery could be performed with optimal local control and reducing distant failure (Green et al., 2005; Ellis et al., 2006; Von et al.,2005; William et al., 2011). Neo adjuvant chemotherapy will also provide a useful biological model to assess the effects of systemic treatment on the primary tumor and regional metastases, in addition to hoping to reduce distant failure.

References

Singletary SE et al., 2002 – *Singletary SE, Allred C, Ashley P et al.* (2002). Revision of the American Joint Committee on Cancer staging system for breast cancer. *J ClinOncol.* 20: 3628–3636.

Cristofanilli M et al., 2003 – *Cristofanilli M, Buzdar Au, Hortobágyi Gn.* (2003). Update on the management of inflammatory breast cancer. *The Oncologist.* 8:141–148

Taylor ME et al., 1997 – *Taylor M.E., Perez C.A. and Levitt S.H.* (1997). Breast: Locally advanced (T3&T4), inflammatory and recurrent tumors. In: Principles and practice of radiation oncology. Ed. Perez C.A. and Brady L.W, 3rd edition. Lippincott-Raven Publishers, Ch.51.

Hortobagyi GN et al., 1995 – *Hortobagyi G.N., Buzdor A.U., Stran E.A., Ames F.C., Singletary S.E.* (1995). Primary chemotherapy for early and advanced breast cancer. *Cancer Lett.* 90 (1): 103-9. Mar.

Seidman Het al., 1987 – *Seidman H, Gelb SK, Silverberg E et al.* (1987). Survival experience in the Breast Cancer Detection Demonstration Project. *CA Cancer J Clin.* 37: 258–290.

Harris JR et al., 1992 – *Harris J.R, And Bonadonna G.* (1992). Cancer of the breast. In cancer. Principles and practice of oncology. Ed DeVita V.T., Hellman S. and Rosenberg S.A., 4th edition Pub. Lippincott Company. Ch., 40.

Wang C et al., 1996 – *Wang H.C. And Lo S.S.* (1996). Future prospects of neoadjuvant chemotherapy in the treatment of primary breast cancer. *Semin. Surg. Oncol.* 12 (1): 59-66, Jan-Feb.

Cuningham JD et al., 1998 – *Cuningham J.D, Weiss S.E, Ahmad S, Bratton J.H, Bleiweiss I.J, Tarter P.I., Brower S.T.* (1998). The efficacy of neoadjuvant chemotherapy compared to postoperative therapy in the treatment of locally advanced breast cancer. Cancer Invest, 16 (2): 86-96.

Karlesson YA et al., 1998 – *Karlesson Y.A., Melstrom P.O., Hatschek T., Fornander T.G., Soderberg M., Bengtsson Y.A., Jansson T.E., Sjoberg S.M., Berg J.C.* (1998). Multimodality treatment of 128 patients with locally advanced breast carcinoma in the era of mammography screening using standard polychemotherapy with 5-FU Epirubicin and cyclophosphamide, prognostic and therapeutic implications. *Cancer*. 83 (5):936-47 Suppl. 1.

Singletary SE et al., 1995 – *Singletary S.E., Hortobagyi G.N., Kroll S.S.* (1995). Surgical and medical management of local-regional treatment failure in advanced primary breast cancer. *Surg. Oncol. Clin. N. Am.* 4 (4): 671-84, Oct.

Ibrahim EM et al., 1999 – *Ibrahim Em., Ezzat A.A., Stuart R.K., Ajarem D.S. And Raja M.* (1999). Stage III breast cancer-single institution experience, Oncology, KFSH, Riyadh, Saudi Arabia, Program/Proceeding of The American Society Of Clinical Oncology, 35th Annual Meeting. Vol. 18, Abstract, (360).

Cancer Incidence SA, 1999 – Cancer Incidence Report, Saudi Arabia (1994-1996), Kingdom Of Saudi Arabia, Ministry Of Health, National Cancer Registry.

Eisten T et al., 1998 – *Eisten T., Smith I.E., Johnston S., Ellis P.A., Prendiville J., Seymourm. T., Walsh G., Ashley S.* (1998). Randomized phase II trial of infusional 5 FU, Epirubicin, and cyclophosphamide versus infusional 5 FU, Epirubicin and cisplatin in patients with advanced breast cancer. *J. Clin. Oncol.* 16 (4): 1350-57, Apr.

Fisher et al., 1998 – *Fisher B., Bryant J., Wol, Ark N., Mamounas E., Brown A., Fisher E.R., Wickerham L.D., Lees A.W., Dimitrov N.V. And Bear H.D.* (1998). Effect of postoperative chemotherapy on the outcome of women with operable breast cancer. J. *Clin. Oncol.* 16 (8):2672-85, Aug.

Kuerer HM et al., 1999 – *Kuerer H.M., Newman L.A., Smith T.L., Ames F.C., Hunt K.K., Buda A.U., Hortobagyi G.N., Singletary S.E. (1999).* Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph nodes response to doxorubicin-based neoadjuvant chemotherapy. *J. Clin. Oncol.* 17 (2):468-96, Feb.

Crow JP et al.,1994 – *Crow J.P., Gordon N.H., Shank R.R., Zollinger R.M., Brumberg D.J., Shuck J.M.* (1994). Age does not predict cancer outcome. *Arch. Surg.* 129 (5): 483-96, May (Abstract).

Newman LA et al.,1998 – *Newman L.A., Kuerer H.M., Singh G., Bucchloz T.A., Hunt K.K., Ames F.C. And Singletary S.E.* (1998). Age-related difference in the utilization and impact of multimodality therapy on the survival of black breast cancer patients. Program/Proceedings of the American Society of Clinical Oncology, 34th Annual Meeting, Vol. 17, Abstract (621), May.

Harris J et al., 1997 – *Harris J., Morrow M., Norton L.* (1997). Malignant tumors of the breast. In: Cancer principles and practice of oncology, Ed. DeVita V.T., Hellman S. and Rosenberg S.A. '5th edition. Lippincott-Raven Publishers, Ch. 36, Sec. 2.

Philiph A et al., 2000 – *Philiph P.A., Penick N.L., Vashanpey an U., Simon M.S., Lorusso P., Chaplan R., Beirmat L. and Flahorty L.E.* (2000). Phase II study of doxorubicin, docetaxel and 5 Fu (FAT) in patients with locally advanced breast cancer. Program/proceedings of the American Society of Clinical Oncology, 36th Annual Meeting, Vol. 19, Abstract (510), May.

Esteva FJ et al., 2000 – *Esteva F.J., Rosoles M.F., Esparazaguerre L.T., Sahin A.A., Soss M.I., Booser D.J., Ibrahim M., Cristofanilli M., Hunt K.K., Horyobagyi G.N.* (2000). Phase II trial of primary chemotherapy with docetaxel and doxorubicin in locally advanced breast cancer-clinical and pathological results. Program/proceedings of the American Society of Clinical Oncology, 36th Annual Meeting, Vol. 19, Abstract (510), May.

Ellis GK et al., 2000 – *Ellis G.K., Green S.J., Livingstone G.T., Budd S.E., Rivkin J.K., Gandura G.R. And Martino S.* (2000). Neoadjuvant doxorubicin, cyclophosphamide and G-CSF (AC+G) for locally advanced breast cancer (LABC) Southwest Oncology Phase II Trial. Program/proceedings of the American Society of Clinical Oncology, 36th Annual Meeting, Vol. 19, Abstract (326), May.

Schwartz GF et al., 1994 – *Schwartz G.F., Birchansky C.A., Komamicky L.T., Mansfield C.M., Cantor R.I., Biermann W.A., Fellin F.M., and Mcfarlane J.* (1994). Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. *Cancer*. 73 (2):362-9, Jan 15.

Murthy SM et al., 1999 – *Murthy S.M., Reid S.E., Jonarden S., Scenlon C.F., Khankar J.D.* (1999). Prevention of breast cancer relapse by neoadjuvant chemotherapy-status of the mechanism. Program /proceedings of the American Society of Clinical Oncology, 36th Annual Meeting, Vol. 18, Abstract (517).

Kent AL et al., 1995 – *Kent A.L., Eaton M., Marshal N., Humeniuk V.* (1995). Locally advanced breast cancer is surgery warranted following, chemotherapy. *Aust. N.Z. J. Surg.,* 65 (4): 229-32, Apr.

Green MC et al., 2005 – *Green Mc, Buzdarau, Smitht et al.* (2005). Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J ClinOncol.* 23: 5983–5992.

Ellis GK et al., 2006 – *Ellis Gk, Green Sj, Russell Ca, et al.* (2006). Swog 0012, a randomized phase III comparison of standard doxorubicin and cyclophosphamide followed by weekly paclitaxel versus weekly doxorubicin and daily oral cyclophosphamide plus G-CSF followed by weekly paclitaxel as neoadjuvant therapy for inflammatory and locally advanced breast cancer. *J ClinOncol.* 24(suppl): 12s. abstr LBA537

Von M et al.,2005 – *Von Minckwitz G, Raab G, Caputo A et al.* (2005). Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: The GEPARDUO study of the German Breast Group. *J ClinOncol.* 23: 2676–2685.

William E et al., 2011 – *William E. Barlow, Julie R. Gralow, Gabriel N. Hortobagyi, B. Christy A, Russell, Melanie, Royce, Edith A. Perez, Danika Lew, Robert B, Livingston* (2011). Phase III Comparison of Standard Doxorubicin and Cyclophosphamide Versus Weekly Doxorubicin and Daily Oral Cyclophosphamide Plus Granulocyte Colony-Stimulating Factor As Neoadjuvant Therapy for Inflammatory and Locally Advanced Breast Cancer: SWOG 0012, *J ClinOncol.* Mar 10; 29(8): 1014–1021.