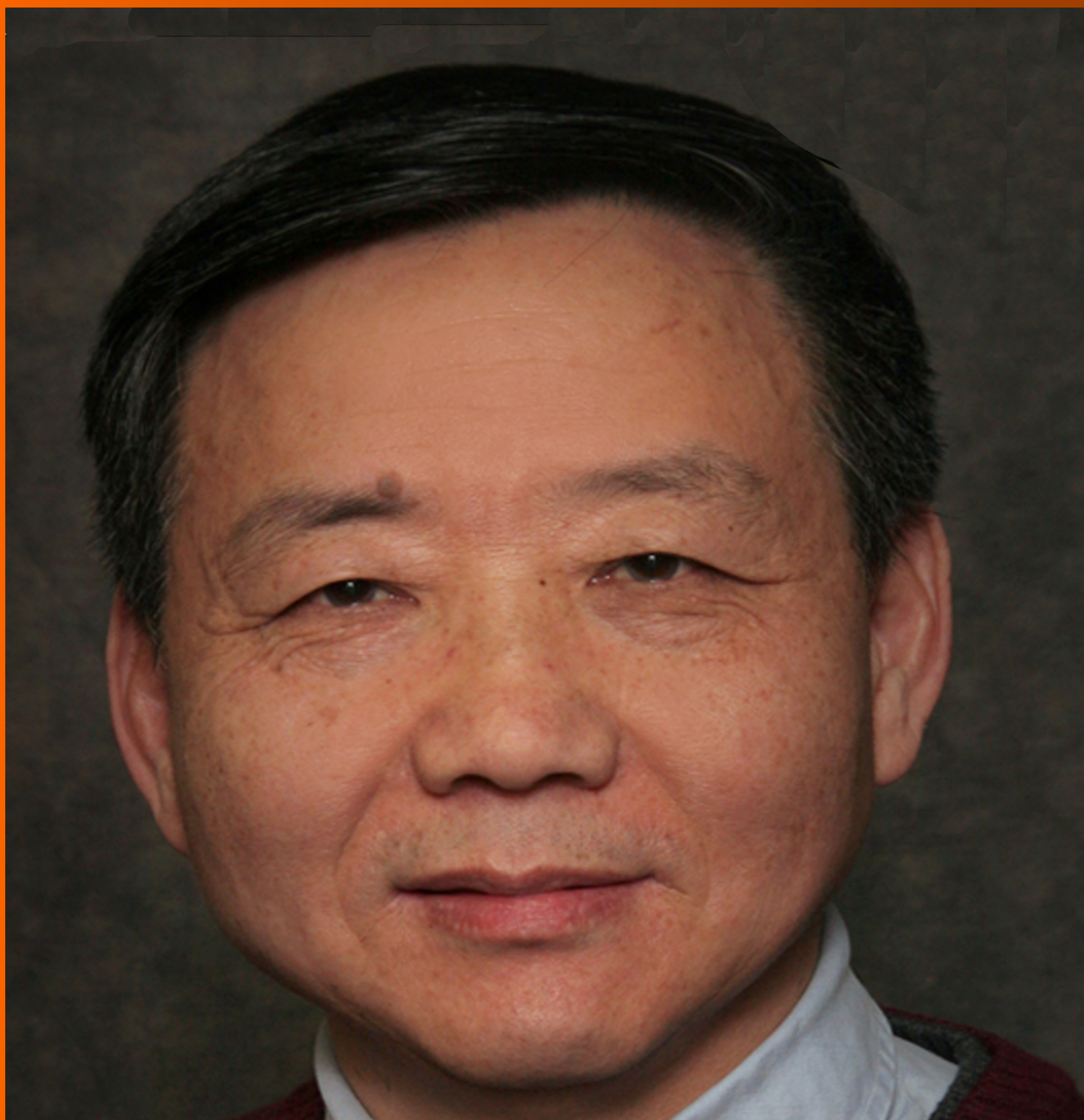


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Epidemic of non-alcoholic fatty liver disease and hepatocellular carcinoma

Adnan Said, Aiman Ghufuran

Adnan Said, Division of Gastroenterology and Hepatology, Department of Medicine, William S. Middleton VAMC, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705, United States

Aiman Ghufuran, Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI 53226, United States

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Correspondence to: Adnan Said, MD, MS, Associate Professor, Division of Gastroenterology and Hepatology, Department of Medicine, William S. Middleton VAMC, University of Wisconsin School of Medicine and Public Health, 4223 MFCB, 1685 Highland Avenue, Madison, WI 53705, United States. axs@medicine.wisc.edu
Telephone: +1-608-2634034
Fax: +1-608-2655677

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Abstract

Non-alcoholic fatty liver disease (NAFLD) associated hepatocellular carcinoma (HCC) incidence is increasing worldwide, paralleling the obesity epidemic. Although most cases are associated with cirrhosis, HCC can occur without cirrhosis in NAFLD. Diabetes and obesity are associated risk factors for HCC in patients. Given the sheer magnitude of the underlying risk factors (diabetes, obesity, non-cirrhotic NAFLD) screening for HCC in the non-cirrhotic population is not recommended. Optimal screening strategies in NAFLD cirrhosis are not completely elucidated with Ultrasound having significant limitations in detection of liver lesions in the presence of obesity and steatosis. Consequently NAFLD-HCC is more often diagnosed at a later stage with larger tumors and reduced opportunities for curative treatments as opposed to HCC in other causes of cirrhosis. When HCC is found at a curative stage treatments including liver transplantation, resection and loco-regional therapies are associated with good results similar to that seen in HCV-HCC. Future strategies under study include the use of chemopreventive and antioxidant agents to reduce development of cirrhosis and non-alcoholic steatohepatitis (NASH). Strategies to reverse NASH *via* weight loss, control of associated conditions like diabetes are key strategies in reducing the increasing incidence of NASH-HCC. Novel therapeutic agents for NASH are in trials and if successful in achieving reversal of NASH will be an important strategy in reducing NAFLD-HCC.

Key words: Non-alcoholic fatty liver disease; Hepatocellular carcinoma; Screening; Epidemiology; Pathophysiology; Diagnosis; Liver transplant; Resection; Locoregional therapy; Treatment

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Core tip: Non-alcoholic fatty liver disease (NAFLD) related hepatocellular carcinoma (HCC) is rapidly increasing worldwide. HCC in NAFLD is often detected at

a more advanced stage than in hepatitis C virus (HCV). Challenges include earlier recognition of cirrhosis in NAFLD to allow earlier screening for liver cancer. NAFLD also has a higher proportion of HCC occurring in the absence of cirrhosis. Given the sheer number of patients with non-cirrhotic NAFLD, screening for HCC in this population is not practical. Instead prevention and treatment of non-alcoholic steatohepatitis to prevent cirrhosis should be an important strategy. When NAFLD-HCC is found at a curative stage, results with liver transplant, resection and loco-regional therapy are similar to that seen in HCV-HCC.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the leading chronic liver disorder in the developed world, with a worldwide prevalence ranging from 6% to 35%^[1]. The incidence of NAFLD is continuing to rise worldwide, paralleling the epidemic of metabolic syndrome worldwide. NAFLD is caused by an insulin-resistant state, occurring in the presence of diabetes, obesity, and metabolic syndrome^[2].

EPIDEMIOLOGY

The incidence of hepatocellular carcinoma (HCC) in the United States and worldwide continues to rise, with an age-adjusted incidence rising from 1.5 to 6.7 per 100000 individuals in the past 30 years^[3,4]. The most recent Surveillance, Epidemiology and End Results (SEER) registry data show that the rates for new liver and intrahepatic bile duct cancer cases have been rising on average 3.0% each year over between 2004 and 2013 (Figure 1)^[5]. Most cases of HCC in the United States occur over age 50, with over 70% of cases occurring in men^[4] and the ethnics groups with the highest incidence rates in the United States are Asian/Pacific Islanders and Hispanics (Table 1)^[6].

In the United States, SEER registries 4929 cases of HCC between 2004-2009 were examined^[7]. 14.1% of HCC were due to NAFLD and between 2004-2009 NAFLD-HCC showed a 9% annual increase. However, the rise in incidence now may be plateauing in the United States^[8].

RISK FACTORS AND PATHOGENESIS

Cirrhosis is the most common underlying cause of HCC, with 80%-90% of patients diagnosed with HCC having underlying cirrhosis^[9]. There is new data emerging to suggest that NAFLD may be an independent risk factor for HCC, even in the absence of cirrhosis^[10-12] (Figure 2).

Diabetes and obesity are known independent risk factors for the development of HCC. There appears to be a common pathway *via* insulin resistance and its subsequent inflammatory cascade in the development of NASH and HCC. HCC is increased in patients with diabetes^[13,14] as well as obesity^[15]. In a prospective United States study of more than 900000 adults, overweight and obesity were associated with excess cancer mortality with an Odds ratio of 4.52 for liver cancer mortality in men and an Odds ratio of 1.68 in women. In a case control study of HCC, diabetes was associated with a 2-3 fold increased risk of HCC regardless of presence of other risk factors^[8].

Genetic polymorphisms (I148M) in the gene encoding patatin-like phospholipase domain-containing protein 3 (PNPLA3) is a known risk factor for histologic steatosis as well as NASH, fibrosis and cirrhosis^[16]. It has now also been shown to be an independent risk factor for development of HCC with a meta-analysis showing that PNPLA3 rs738409 SNP is associated with an Odds ratio of 1.40 for HCC in cirrhosis including NAFLD^[17]. The common genetic mutations of hemochromatosis (C282Y and H63D) have been implicated in risk of developing NAFLD and HCC as well. In a recent meta-analysis a significantly increased risk of NAFLD and HCC was discovered. H63D polymorphism was associated with increased risk of developing non-cirrhotic HCC in the African population^[18]. Putatively this is due to increased iron overload leading to hepatic inflammation, fibrosis and carcinogenesis.

Insulin resistance also leads to release of free fatty acids (FFA) and other reactive oxygen species that cause oxidative stress and inflammation. Trans-4-hydroxy-2-nonenal, a product of lipid peroxidation has been shown to cause mutations of the p53 tumor suppressor gene that is associated with more than half of human cancers including HCC^[11]. The inflammation caused by oxidative stress leads to an increased release of inflammatory and inhibitory cytokines including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and nuclear factor kappa B (NF- κ B)^[19]. Presence of these chemical mediators leads to hepatocyte death, compensatory proliferation, and ultimately carcinogenesis.

Leptin is a pro-inflammatory adipokine that is elevated in patients with NAFLD^[20]. Leptin is associated with increasing expression of pro-inflammatory cytokines like TNF- α and IL-6^[21], and activation of Janus Kinase (JAK)^[22]. It can cause tumor growth and has been associated with HCC recurrence after treatment^[23]. Adiponectin is an anti-inflammatory adipokine that has been shown to inhibit angiogenesis *via* modulation of apoptosis in an animal model. Adiponectin deficiency in obese states has been linked to carcinogenesis^[24]. It is specific to adipose tissue and is decreased in insulin-resistant states, and thus may potentially play a role in development of HCC.

HCC IN NAFLD WITH ADVANCED FIBROSIS

NAFLD associated HCC occurs in patients with cirrhosis

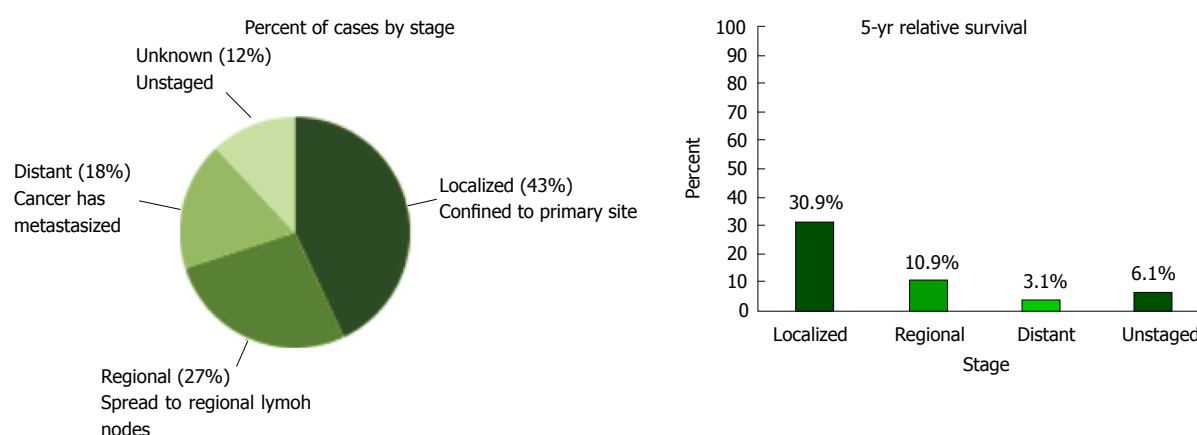


Figure 1 Percent of cases and 5-year relative survival by stage at diagnosis: Liver and intrahepatic bile duct cancer.

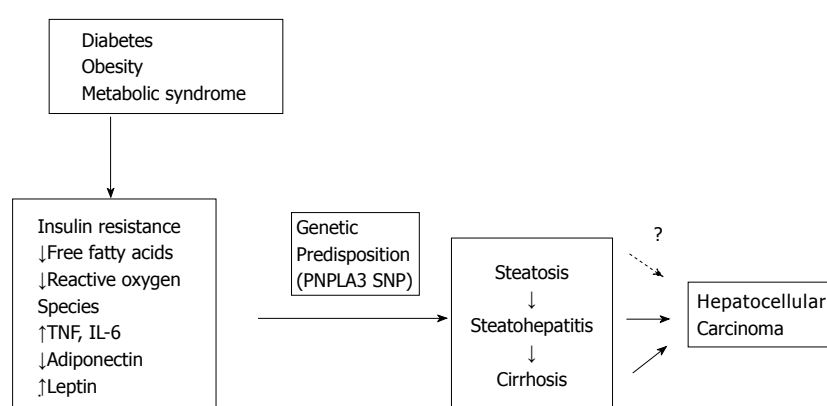


Figure 2 Development of hepatocellular carcinoma in non-alcoholic fatty liver disease.

at variably reported rates. A single center cohort study reported HCC at an annual incidence of 2.6%^[25] compared to a 4% incidence in those with hepatitis C related cirrhosis. Other studies have reported overall incidence of HCC in NAFLD Cirrhosis from 2.4% at 7 years to 12.8% over 3 years^[26].

Given the rising incidence of NAFLD, and the advances in curative options for Hepatitis C infection, NAFLD is expected to become the leading cause of HCC in developed nations^[10]. Known risk factors for HCC in cirrhotic NAFLD include male gender, age over 70, and underlying diabetes and hypertension^[27].

HCC IN NAFLD WITHOUT ADVANCED FIBROSIS

There is increasing evidence to suggest that NAFLD contributes to non-cirrhotic HCC as well^[10]. Also, while the presence of hepatic steatohepatitis is an established risk factor for development of cirrhosis and HCC^[28], there are case reports of HCC complicating underlying NAFLD in the absence of hepatitis or advanced fibrosis, making associations between steatosis, steatohepatitis, cirrhosis, and HCC complex^[10].

While several studies have reported HCC in non-cirrhotic NAFLD the risk seems to be lower (0% to 3%

over 20 years)^[26]. Recent studies however have shown that non-cirrhotic HCC may be more common in NAFLD compared to other chronic liver diseases. Studies from multiple countries including United States, Japan and France of NAFLD-associated HCC have shown that a significant proportion of HCC occurs in the absence of cirrhosis in NAFLD. In a histologic analysis of resected NAFL-HCC from France the majority of patients did not have cirrhosis and 65% had stage 0-2 fibrosis^[29]. In the study from Japan of 87 HCC patients only 51% had histologic cirrhosis and 28% had stage 1-2 fibrosis only^[27]. In a United States veterans Study of 1500 HCC cases, 8% of the HCC cohort had NAFLD associated HCC and only 65% of the NAFLD-HCC cohort had cirrhosis (NAFLD had > 5 fold risk of HCC without cirrhosis compared to HCV related cirrhosis^[30].

Several large-scale epidemiological studies have shown that there is a higher incidence of HCC in patients with obesity and diabetes, as well as poorer outcomes^[10]. The relative risk of liver cancer was 117% for overweight subjects and 189% for the obese^[31], while risk of mortality in men with a BMI > 35 kg/m² can be as high as 4.5 times that in men with a normal BMI^[15]. Similarly, presence of diabetes alone increases the risk of development of HCC three-fold^[8]. Other independent risk factors for HCC in NAFLD include

Table 1 Age-adjusted hepatocellular carcinoma incidence and liver cancer mortality rates per 100000 persons, 2006-2010^[51]

Outcome	Age (yr)	All races		None-hispanic						Hispanic	
		Rate	95%CI	White		Black		API		Rate	95%CI
				Rate	95%CI	Rate	95%CI	Rate	95%CI		
HCC	Overall	5.9	(5.8-5.9)	4.2	(4.2-4.3)	7.5	(7.3-7.8)	11.7	(11.3-12.0)	9.5	(9.3-9.8)
Incidence	35-49	2.2	(2.1-2.3)	1.4	(1.3-1.5)	2.5	(2.2-2.8)	4.7	(4.3-5.2)	3.2	(2.9-3.4)
SEER 18	50-64	16.5	(16.2-16.8)	12.2	(11.9-12.6)	26.9	(25.8-28.1)	23.5	(22.4-24.7)	24.3	(23.3-25.3)
	> 65	22.3	(21.9-22.7)	16.0	(15.5-16.4)	22.4	(20.9-23.9)	54.7	(52.4-57.0)	40.5	(38.7-42.4)
Liver cancer	Overall	4.3	(4.3-4.3)	3.6	(3.5-3.6)	6.4	(6.3-6.6)	8.2	(7.9-8.4)	7.0	(6.9-7.2)
Mortality	35-49	1.2	(1.2-1.2)	0.9	(0.8-0.9)	2.0	(1.9-2.2)	2.8	(2.6-3.1)	1.4	(1.3-1.5)
US	50-64	9.7	(9.5-9.8)	7.7	(7.6-7.8)	18.6	(18.2-19.1)	13.0	(12.4-13.6)	13.5	(13.0-13.9)
	> 65	20.1	(19.9-20.3)	17.2	(17.0-17.5)	24.5	(23.7-25.3)	43.2	(41.6-44.8)	36.7	(35.6-37.8)

API: Asians and Pacific Islanders; HCC: Hepatocellular carcinoma; SEER: Surveillance, Epidemiology and End Results.

polymorphisms in the PNPLA3 gene (I148M)^[32]. In the most recent met-analysis, HFE mutation (C282Y and H63D) was also shown to be associated with HCC risk in NAFLD populations including for the H63D mutation in non-cirrhotic African populations^[18].

CLINICAL PRESENTATION AND DIAGNOSIS

In the US SEER registries 4929 cases of HCC between 2004-2009 were examined^[7]. Fourteen point one percent were due to NAFLD. Patients with NAFLD-HCC were older, had more advanced tumor stage at presentation and had shorter survival time and were less likely to receive a liver transplant.

These findings are seen in non-United States centers as well. In a large retrospective cohort study from Germany, of 1119 patients with HCC, those with NASH-HCC were older, had higher metabolic complications but better liver function at presentation^[33]. Resection was performed in only 17.8% and transplant in 4.4% of these patient and overall survival for NAFLD-HCC was lower than that for HCV-HCC.

An Italian multicenter observational study of NAFLD-HCC vs HCV-HCC was performed^[34]. Compared to HCV-HCC, NAFLD-HCC was more again likely associated with larger tumors, more infiltrative tumors and was more likely to be detected outside surveillance. Survival was significantly shorter in NAFLD-HCC (25.5 mo vs HCV-HCC (33.7 mo) regardless of tumor stage. However analysis of patients with HCC in Milan criteria sent for curative treatments showed similar survival in NASH-HCC and HCV-HCC (38.6 mo vs 41 mo).

In a study from 2 centers in the United Kingdom, 275 HCV related HCC patients were compared with 212 NAFLD related HCC patients. Patients with NAFLD-HCC had lower rates of cirrhosis and were significantly older and had larger tumors than those with HCV-HCC. Those with NAFLD-HCC were less likely to receive curative therapy than HCV-HCC including liver transplant (21/212 of NAFLD-HCC) vs 80/275 of HCV-HCC. Despite this overall survival from diagnosis was similar for NAFLD-HCC (56% at 1year and 23% at 3 years) and HCV-HCC

(58% at 1 year and 21% at 3 years)^[35].

The reasons for these tumor stage differences are multi-factorial. The current AASLD Guidelines recommend that patients with cirrhosis undergo regular surveillance for HCC with ultrasound every 6 mo^[36]. While this may suffice in most patients with cirrhosis, patients with NASH are often obese, thus limiting the diagnostic ability of ultrasound^[37]. The ITALICA study group showed that HCC was significantly less likely to be diagnosed during surveillance in patients with cryptogenic cirrhosis compared to HCV patients, translating into a greater prevalence of advanced HCC stage and poor survival^[38]. MRI, therefore, may offer a better enhanced surveillance for HCC but comes at a higher cost and reduced accessibility.

Underdiagnosis of cirrhosis is a common problem as it leads to lack of screening and potentially increased stage of HCC when diagnosed resulting in worse outcomes. In a large cohort of HCC patients (1201) in the VA, 24.6% had undiagnosed cirrhosis prior to HCC diagnosis and patients with NAFLD had higher odds of having undiagnosed cirrhosis (OR = 4.77)^[39].

HCC TREATMENT IN NASH

Similar to other causes of HCC, NAFLD associated HCC occurs in the context of liver disease and liver function and portal hypertension are integral in multimodality assessment and treatment of HCC.

In addition to actual tumor stage, the severity of liver impairment also affects the available options for management of HCC. Thus, the most commonly used schema for management of HCC is Barcelona Clinic Liver Cancer (BCLC)^[36,40] which incorporates both stage of the tumor as well as disease severity of underlying liver impairment (Figure 3)^[36].

As per current SEER data, 42.9% of patients with HCC are diagnosed at the local stage, and the 5-year survival for localized liver and intrahepatic bile duct cancer is 30.9%^[5]. Curative therapies include resection for early stage HCC with thermal ablative therapies also showing comparable results for single small tumors. Liver transplantation is a good option for patients with Milan (T2) criteria tumors who have complications of

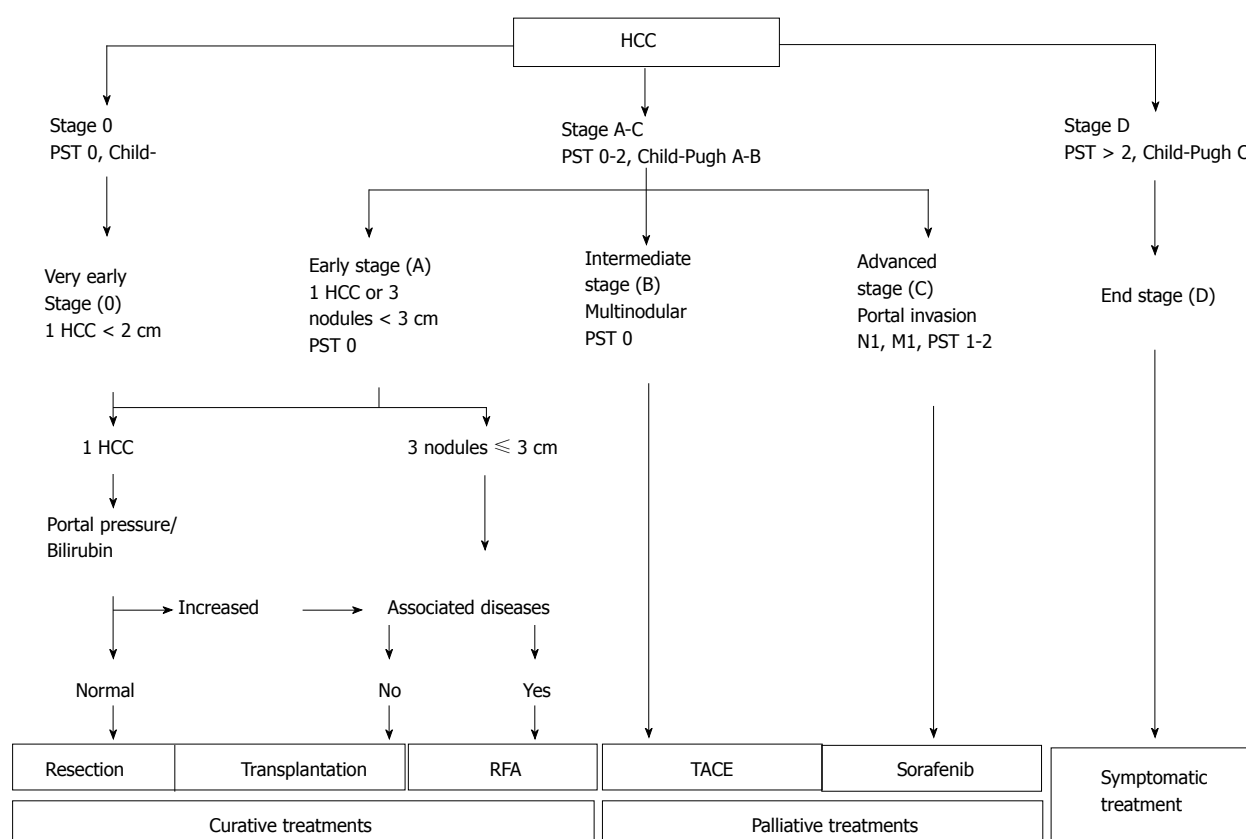


Figure 3 Barcelona clinic liver cancer staging system^[36]. HCC: Hepatocellular carcinoma; TACE: Trans-arterial chemoembolization.

cirrhosis and portal hypertension^[41].

Patients with larger tumors can be candidates for intra-arterial therapy including trans-arterial chemoembolization (TACE) and Y-90 radioembolization that are utilized with goals of tumor control and not always for potentially curative ends. Thus finding tumors that are small and limited to the liver offers patients the widest array of potential treatments and hope of cure^[42].

Liver transplant and resection

With the growing epidemic of NAFLD, NAFLD associated HCC is the second most common indication for liver transplant (LT) for HCC in the United States after HCV since 2006, increasing 4 fold since 2002^[43]. In this study, Wong *et al*^[43] analyzed 10061 patients with HCC who underwent LT for HCC between 2002-2012. Since MELD system was implemented in 2002, HCC related liver transplants increased significantly from 3.3% ($n = 143$) of all LT in 2002 to 23.3% ($n = 1336$) in 2012. NASH related HCC also increased significantly from 8.3% of all HCC related LT in 2002 to 13.5% in 2012 and were the second leading reason for HCC related LT behind HCV.

In a study from 2 United Kingdom liver transplant centers between 2000 and 2014, 487 patients with HCC associated with NAFLD or HCV presented to the transplant centers. 275 had HCC secondary to HCV and 212 secondary to NAFLD^[35]. Patients with NAFLD were significantly older than HCV patients at time of

HCC diagnosis (69.6 years vs 58.6 years). Absence of cirrhosis was more common in NAFLD patients (13%) vs HCV patients (1%). The non-cirrhotic patients were more likely to be older, have DM and had larger tumor size (likely due to non-surveillance). NAFLD patients had significantly larger tumors at presentation and were less likely to receive liver transplant than HCV-HCC patients and were more likely to receive TACE. Overall survival was however similar between NAFLD and HCV HCC at 3 years from diagnosis (21% and 23%).

Outcomes for LT for NAFLD-HCC were compared in a US study with LT for HCC-HCV and HCC-ALD. Over a 50 mo median follow up there was no difference in tumor free survival and overall survival (curative treatments vs HCV, ALD)^[44].

In an Italian study that compared resection in HCC-associated with metabolic syndrome with HCC-HCV outcomes were similar in 96 HCC-Metabolic Syndrome and 96 HCC-HCV patients after resection. All patients had Child A cirrhosis and operative mortality was 2.1% (similar between the 2 groups). Morbidity and liver failure rates were also similar and were impacted by cirrhosis need for major hepatectomy and MELD score but not by histologic steatohepatitis. Five year overall survival was better in HCC-Metabolic Syndrome vs HCC-HCV (65.6% vs 61.4%, $P = 0.03$)^[45].

Reddy *et al*^[44] reported 3-year survival after resection was better in NASH vs HCV-ALD patients (60.9% vs 36.2%) including on multivariable analysis. Therefore

curative treatments like resection are an acceptable treatment for NASH patients.

Locoregional therapies

Liver-directed therapy with percutaneous ablation is a frontline therapeutic option in patients with HCC in its early stage. These options include ablation by chemical agents (acetic acid or ethanol) or by heat (radiofrequency, microwaves, laser, or cryotherapy). The efficacy of these therapies is followed by contrast-enhanced CT scan, with lack of contrast uptake suggestive of adequate response^[36]. NASH-HCC outcomes with ablation are reported to be as efficacious as HCV-HCC or ALD-HCC^[44].

Non-curative options

TACE and Sorafenib are available non-curative options for HCC^[36,40]. TACE may sometimes be employed to downstage a tumor prior to use of transplantation as a curative option.

Chemoprevention

Given the current limitation in treatment options, there is currently an interest in targeting the known molecular pathways as treatment options for HCC. NAFLD and obesity associated HCC has been linked to oxidative stress, hyperinsulinemia, and chronic inflammation. Addressing metabolic syndrome can be a preventative measure against development of HCC. These options include, but are not limited to, exercise, weight loss, and optimal control of diabetes, and hypertension, if present. In fact, one study showed a lower relative risk of developing HCC in vigorously active subjects compared to those with a sedentary lifestyle^[46]. This reduction in risk was found to be independent of BMI.

In preliminary studies, dietary antioxidants like, vitamin C and E, selenium and coenzyme Q, vitamin D supplementation, and a Mediterranean diet have been shown to prevent hepatic carcinogenesis^[47]. This is of particular interest given the known role of antioxidants in limiting and even reverting fibrosis in patients with NASH^[48]. Similarly, the use of metformin, known to reduce insulin resistant and subsequent steatohepatitis, has been shown to be associated with reduced incidence of HCC in diabetic patients^[47].

In animal models anti-inflammatory and anti-oxidant compounds like green tea, BCAA and acyclic retinoids have shown promise in preventing HCC. BCAA supplementation in cirrhosis is associated with improvements in insulin resistance and inhibition of IGF-1 and IGF-2 expression in the db/db obese mouse liver and reduced expression of liver cancers^[49]. In Human study long term supplementation with BCAA reduced HCC in obese patients with cirrhosis^[50]. Green tea extracts have been associated with beneficial effects on weight loss, insulin resistance and inflammatory cytokines in animal models^[51]. In animal models beneficial effects on carcinogenesis have been reported as well by modulation of tyrosine kinase and Pi3/AKT pathways^[52] and in reducing hepatic tumors in DEN treated db/db/mice.

With green tea extracts no human data have been published showing efficacy. Acyclic Retinoids derivatives of vitamin A exert their effect through nuclear receptors including RXRalpha, which is found in abundant supply in human liver. Supplementation of retinoids has shown beneficial effects in maintaining hepatocyte homeostasis in hepatocyte carcinogenesis^[53]. In a long term human study acyclic retinoids reduced the chance of HCC recurrence and death by 40%^[54]. Given the significant association of diabetes with HCC, metformin has been studied in cohort and case-control studies and a meta-analysis showed a significantly reduced risk of HCC with metformin use in diabetics^[55].

CONCLUSION

In summary, there is indisputable evidence showing the increased risk of HCC in patients with NAFLD regardless of the presence of advanced fibrosis and steatohepatitis. Patients with HCC and NAFLD are increasing more rapidly than any other indication for liver transplantation. Patients with NAFLD are candidates for curative and non-curative therapies with encouraging results.

Diagnosing HCC in advanced stages of tumor or liver disease can render curative options futile and call for development of alternate guidelines for enhanced HCC surveillance in patients with metabolic syndrome. The current challenges include developing optimal surveillance options in targeted populations. There is also a huge potential in development of therapies targeting NASH and molecular pathways as preventive options for HCC in patients with cirrhosis in general and NAFLD in particular.

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Metronomic chemotherapy for non-metastatic triple negative breast cancer: Selection is the key

Connie Rabanal, Rossana Ruiz, Silvia Neciosup, Henry Gomez

Connie Rabanal, Rossana Ruiz, Silvia Neciosup, Henry Gomez, Department of Medical Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

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Correspondence to: Connie Rabanal, MD, Department of Medical Oncology, Instituto Nacional de Enfermedades Neoplasicas, Av. Angamos Este 2520 Surquillo, Lima 15038, Peru. crabanal@auna.pe
Telephone: +51-1-921139544

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Abstract

Triple negative breast cancer (TNBC) accounts for 15%-20% of all breast cancer, and is still defined as what it is not. Currently, TNBC is the only type of breast cancer

for which there are no approved targeted therapies and maximum tolerated dose chemotherapy with taxanes and anthracycline-containing regimens is still the standard of care in both the neoadjuvant and adjuvant settings. In the last years, metronomic chemotherapy (MC) is being explored as an alternative to improve outcomes in TNBC. In the neoadjuvant setting, purely metronomic and hybrid approaches have been developed with the objective of increasing complete pathologic response (pCR) and prolonging disease free survival. These regimens proved to be very effective achieving pCR rates between 47%-60%, but at the cost of great toxicity. In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, more promisingly, as maintenance therapy for high-risk patients, especially those with no pCR after neoadjuvant chemotherapy. Considering the dismal prognosis of TNBC, any strategy that potentially improves outcomes, specially being the oral agents broadly available and inexpensive, should be considered and certainly warrants further exploration. Finally, the benefit of MC needs to be validated in properly designed clinical trials where the selection of the population is the key.

Key words: Metronomic chemotherapy; Triple negative breast cancer; Neoadjuvant; Adjuvant; Maintenance

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Core tip: Triple negative breast cancer (TNBC) is the only type of breast cancer for which there are no approved targeted therapies. Metronomic chemotherapy (MC) is being explored as an alternative to improve outcomes in TNBC. In neoadjuvant setting, purely metronomic and hybrid approaches achieve complete pathologic response (pCR) rates between 47%-60%, but at the cost of great toxicity. In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, promisingly, as maintenance therapy for high-risk patients, especially those with no pCR. Considering the dismal prognosis of TNBC, any

strategy that improves outcomes, specially being broadly available and inexpensive, should be considered.

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INTRODUCTION

Triple negative breast cancer (TNBC) accounts for 15%-20% of all breast cancer cases and is still defined as what it is not^[1]. This entity is a molecularly heterogeneous and generally aggressive disease with poor survival^[2]. Currently, TNBC is the only type of breast cancer for which there are no approved targeted therapies and maximum tolerated dose (MTD) chemotherapy with taxanes and anthracycline-containing regimens is still the standard of care in both the neoadjuvant and adjuvant settings^[3]. Nowadays, there is no evidence that prolonging treatment or escalating doses confers any benefit^[4].

In the last years, aiming to improve responses in TNBC and because of the lack of target therapies, metronomic chemotherapy (MC) has been explored. In the neoadjuvant setting, purely metronomic and hybrid (approach which includes combined MTD chemotherapy with MC) neoadjuvant regimens, have been developed with the objective of increasing pathologic complete response (pCR) and prolonging disease free survival (DFS).

In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, more interestingly, as maintenance therapy for high-risk patients, especially those with no pCR after neoadjuvant chemotherapy.

This review outlines the rationale, preclinical data and relevant clinical trials of MC for TNBC as a promising alternative in selected populations, considering its economic viability for our health system care.

UNDERSTANDING METRONOMIC CHEMOTHERAPY

The term MC was first used by Hanahan in 2000, referring to the "close, regular administration of a chemotherapeutic drug for a long time with no extended drug-free breaks"^[5]. It was originally conceived as a strategy to break resistance to chemotherapy by targeting the tumor vasculature instead of the tumor cells^[5].

MTD-based conventional chemotherapy regimens aim to eliminate as many tumor cells as possible by causing direct or indirect damage to their DNA, and thus disrupting its replication in proliferating cells. Due to the low proliferation index of endothelial cells,

conventional MTD chemotherapy causes very limited damage on them^[6,7]. Moreover, as the antiangiogenic effect is not sustained, endothelial cells recover during the rest periods, supporting tumor regrowth and therefore contributing to tumor resistance. Using drugs at a low dose, decreases toxicity and allows continuous administration to overcome this effect^[8]. It has also been reported that in mice with tumor resistance to MTD chemotherapy, exposure to the same drugs, at lower but frequent doses, can achieve a response^[9].

One disadvantage of this regimen is the empiricism in finding the optimal "low dose" or "optimal biologic dose" (OBD)^[10]. Shaked *et al*^[11] have investigated pharmacodynamic cellular biomarkers for determining OBD of different metronomic regimens based in sustained declines in circulating VEGFR-2⁺ endothelial progenitor cells induced by prolonged daily low dose metronomic chemotherapy.

In Table 1, we compare MTD chemotherapy vs MC. MC is considered as a multi-mechanism therapy.

Inhibition of angiogenesis

The benefit of MC is mainly attributed to its direct activity on the drug-sensitive tumor endothelial cells. MC has been shown to reduce the angiogenic potential by decreasing in levels and viability the sustained of bone marrow – derived endothelial progenitor cells, producing vessel normalization, increasing tumor perfusion and thrombospondin 1 (THBS-1) which is an antiangiogenic glycoprotein responsible of inhibiting the circulating endothelial cell^[12,13].

In animal models, it has been demonstrated that low dose cyclophosphamide induces apoptosis in endothelial cells of the tumor microvasculature, compromising DNA repair processes, and therefore inducing a prolonged antiangiogenic effect^[8]. Also, Browder *et al*^[14] showed metronomic cyclophosphamide (CTX) was effective against drug-resistant lung and breast carcinoma cell lines.

Activation of immunity

It is a well-known fact that tumor cells escape from the immune system surveillance and that immuno-suppression caused by chemotherapy, contributes to tumor growth^[15]. Nevertheless, it has been recently suggested that certain cytotoxic drugs such as cyclophosphamide, anthracyclines and taxanes may also have immuno-stimulatory properties, specifically due to their effect on regulatory T (T-reg) cells which are CD4⁺CD25⁺ lymphocytes enriched with tumor necrosis factor receptor (TNF) and cytotoxic T lymphocyte associated antigen 4 (CTLA4)^[16].

T-reg cells inhibit immune responses depending on cytokines and on antigen-specific-dependent processes^[17]. In particular, they suppress lymphocytes CD8⁺, CD4⁺ T helper and natural killer T cells^[17]. It has been demonstrated that T-reg cells increase alongside tumor upstaging and their presence is associated to

Table 1 Comparing maximum tolerated dose chemotherapy *vs* metronomic chemotherapy

	Maximum tolerated dose chemotherapy (conventional)	Metronomic chemotherapy
Dose	High doses	Low doses or biologic optimal doses
Administration	Administered at defined intervals (3 weekly, weekly) determined by the recovery of bone marrow	Dosing frequency is continuous (weekly, every other day, daily)
Plasma concentration	Rise and fall of the plasma concentration of the drug	Sustained plasma concentration of the drug
Target	Proliferating tumor cells	Endothelial cells in the growing vasculature of the tumor
Toxicity	Acute and cumulative toxicity is a concern	Acute toxicity is rare. Cumulative toxicity is unknown, except for etoposide (related to leukemia)

poor response to treatment^[18]. In comparison with tumors exposed to MTD regimens, those exposed to MC exhibit a markedly reduced number of T-reg cells^[19]. Tanaka *et al.*^[20] analyzed the activity of 54 different drugs effect *in vitro* dendritic cells, concluding that vinblastine, etoposide and paclitaxel, administered in low doses, decreased the levels of T-reg cells and delayed tumor progression.

Induction for tumor dormancy

Tumor dormancy was defined by Willis in 1940s and redefined by Hadfield in the early 1950s as a temporary mitotic and growth arrest^[21]. Dormant cells are present in the early phase of tumor progression or after completing treatment. In the early phase, epithelial pre-invasive lesions can undergo epithelial-mesenchymal transition, and then acquire metastatic growth capacity after long periods of dormancy^[22]. After completing treatment, dormant tumor cells may be the source of tumor recurrence, suggesting that these could become refractory to conventional treatment^[23,24]. Folkman *et al.*^[25] showed that metronomic activity induces tumor dormancy, being this the predominant mechanism involved in maintaining the avascular phase. So, when a tumor escapes from the immune surveillance, MC can inhibit tumor development and achieve a long-term control of the disease^[26].

The “4D” Effect

Clinical studies demonstrated that a long exposure to one or more agents and deprivation of others, introducing break periods of MTD with MC, may increase treatment efficacy. This phenomenon is named 4D effect or drug-driven dependency/deprivation effect^[27,28]. André *et al.*^[29] postulated that tumor cells become dependent on chemotherapeutic agents during long exposures and sudden withdrawal or replacement therapy may lead to cell death.

METRONOMIC CHEMOTHERAPY IN TNBC

Neoadjuvant setting

Specially in TNBC, neoadjuvant chemotherapy is effective in down staging the tumor, therefore allowing breast conserving procedures or surgery in initially irresectable

tumors. Additionally, neoadjuvant chemotherapy permits an early evaluation of the effectiveness of systemic therapy *in vivo*. Achieving a pCR is a surrogate marker for prolonged DFS, and less local and distant recurrence^[30,31].

For TNBC, MTD chemotherapy based in anthracyclines and taxanes is still the standard of care. The rate of pCR with this combination ranges between 20% and 39%^[32]. In the most successful experience, von Minckwitz *et al.*^[33] reported a pCR of 39% in 509 patients treated with TAC (docetaxel/doxorubicin/cyclophosphamide). The rate of pCR has been reported to further increase with the addition of platinum salts. Nevertheless, an important proportion of patients would still have residual disease at the end of neoadjuvant treatment. In order to improve the results, several groups have tried to intensify the induction chemotherapy regimens by incorporating metronomic principles. These schemes use conventional drugs at metronomic doses or combine MTD chemotherapy with MC in a hybrid approach (Table 2).

Metronomic-only approach

Interestingly the studies presented below incorporate platinum salts to conventional drugs in a metronomic approach. It should be recalled, that although the GeparSixto results demonstrated that platinum salts increase responses, this practice is still not a standard for TNBC^[33].

A small phase II trial NCT00542191, recently presented at ASCO 2016, used weekly doxorubicin and daily oral cyclophosphamide followed by weekly paclitaxel and carboplatin as neoadjuvant treatment in 18 patients. The pCR rate was 47.6% with a 5-year Overall Survival (OS) of 90% for those who achieved a pCR vs 12.5% for those who did not. However, 62% of patient experienced grade (G) 3 or G4 neutropenia, 24% febrile neutropenia, 12 patients discontinued treatment due to related toxicities and 3 died before completing treatment^[34]. A similar regimen was previously tested by Tiley in 2012, achieving a pCR of 46% (40% pCR, 6.6% CR with foci of ductal carcinoma in situ). Granulocyte colony stimulating factor was added for absolute neutrophil count (ANC) \leq 1000. Main toxicities were related to myelosuppression and two patients came off study due to prolonged neutropenia. Five patients had G4 neutropenia, 1 patient experienced G3 thrombocytopenia, and 1 developed G3 neuropathy^[35]. Although their effectiveness, toxicity represented a major

Table 2 Neoadjuvant metronomic chemotherapy in triple negative breast cancer

	Ref.	Type of study	n	Patient characteristic	Regimens	pCR	Adverse events
Only MC	Hildebrand <i>et al</i> ^[34] 2016	Single arm phase II	18	TNBC, ≥ T2 T4: 5 patients Node +: 12 patients EC II: 47.4% EC III: 28.6%	Part 1 (12 wk) Weekly DX 24 mg/m ² IV Daily CTX 60 mg/m ² PO Followed by Part 2 (12 wk) Weekly PTX 80 mg/m ² IV Weekly C 2AUC IV	47.60%	Neutropenia G3-G4: 62% Febrile neutropenia: 24%
	Tiley <i>et al</i> ^[35] 2012	Single arm phase II	17	TNBC, T2-T4, N0-N1 Median age: 45 yr (25-83) Inflammatory breast cancer: 3	Part 1 (12 wk) Weekly DX 24 mg/m ² IV Daily CTX 60 mg/m ² PO Followed by Part 2 (12 wk) Weekly PTX 80 mg/m ² IV Weekly C 2AUC IV	46.60%	Thrombocytopenia G3: 5% Neutropenia G4: 29% Neuropathy G3: 5%
	Ignatova <i>et al</i> ^[36] 2016	Single arm phase II	40	TNBC cT2-4, N2-3, M0 Median age: 50 yr (27-69) Histologic grade 3: 33.3% Ki67 > 20%: 100%	Part 1 (9 wk) Weekly PTX 60 mg/mm ² IV Weekly C 2AUC IV Then followed by Part 2 (9 wk) Weekly DX 25 mg/m ² IV Daily CTX 50 mg bid PO Daily X 500 mg tid PO	60%	Neutropenia G3-4: 22.2% Mucositis 8.3% Hand-foot syndrome G3: 5.6%
Hybrid	Masuda <i>et al</i> ^[37] 2014	Single arm phase II	40	ER < 10%, T2-T4, N0-N1 Median age 52 yr (33-69) N1: 40% ER < 10%: 17.5% EC I: 12.5% EC II: 77.5% EC IIIA: 10%	Part 1 (4 Cycles every 21 d) Day 1, 7, 14 PTX 80 mg/m ² IV Daily CTX 50 mg PO Daily X 1200 mg PO Followed by Part 2 (4 Cycles every 21 d) Day 1 5-FU 500 mg/m ² IV Day 1 E 100 mg/m ² IV Day 1 CTX 500 mg/m ² IV	47.50%	Neutropenia G3-4: 35% Hand foot syndrome G3-4: 8%
	Cancello <i>et al</i> ^[38] 2015	Single arm phase II	34	ER ≤ 10%, PR ≤ 10%, Her2- Median age: 45 yr (31-64) Premenopausal: 73% EC II: 35% EC III: 67% Histologic grade 3: 82%	Part 1 (4 cycles every 21 d) Day 1 5-FU 200 mg/m ² per day continuous Day 1, 2 E 25 mg/m ² IV Day 1, P 60 mg/m ² IV Followed by Part 2 (three cycles every 28 d) Day 1, 7, 14 PTX 90 mg/m ² Daily CTX 50 mg/d	56%	Neutropenia G3-4: 38% Anemia G3-4: 3%

EC: Clinical stage; ER: Estrogen receptor; DX: Doxorubicin; CTX: Cyclophosphamide; PTX: Paclitaxel; C: Carboplatin; X: Capecitabine; 5-FU: 5-fluoracil; E: Epirubicin; P: Cisplatin; pCR: Pathologic response; TNBC: Triple negative breast cancer; MC: Metronomic chemotherapy.

limitation for both trials.

Ignatova *et al*^[36], added capecitabine and carboplatin to an anthracycline and taxane metronomic regimen, achieving pCR in 60% of patients, the highest pCR rate reported to date with MC. Forty patients with locally advanced TNBC (cT2-T4 N2-3 M0) were treated with metronomic weekly paclitaxel plus carboplatin for 9 wk, followed by weekly doxorubicin, daily oral cyclophosphamide and capecitabine for another 9 wk. Dose limiting toxicities were neutropenia G3 (22%), mucositis G3 (8%) and hand-foot syndrome G3 (5.6%).

Hybrid approach: MTD plus MC

Masuda *et al*^[37] conducted a phase II study that included 40 patients with TNBC or low hormonal receptor BC

treated with 4 cycles of weekly paclitaxel plus daily oral cyclophosphamide and capecitabine, followed by 4 cycles of FEC (5-FU/epirubicin/cyclophosphamide) every 3 wk. Importantly, this regimen achieved a pCR rate of 47.5% and breast preservation in 72.7% of cases. Adverse events (AE) related were G3-4 neutropenia and hand-foot syndrome, in 35% and 8% of cases, respectively^[37].

Cancello *et al*^[38] evaluated the efficacy of a neo-adjuvant regimen in terms of Ki-67 variation, clinical response and toxicity in 34 patients with HER2-negative, ER and PR < 10% BC. Chemotherapy consisted of 4 rounds of ECF (epirubicin/cisplatin/5-FU) every 21 d followed by weekly paclitaxel every 28 d for 3 courses concomitantly with metronomic oral

cyclophosphamide. Importantly, response to treatment was obtained in 91% of patients and 56% achieved a pCR. Also, a 41% difference in the percentage of Ki-67 positive cells was found between the surgical specimens and the pretreatment tumor core biopsy for the entire population (95%CI: 30-51; $P < 0.0001$) vs 22% for those who did not achieve a pCR (95%CI: 7-38; $P = 0.0097$). AE of grade 3 or more included neutropenia in 38% and anemia in 3%. The authors concluded that neoadjuvant ECF regimen followed by weekly paclitaxel with metronomic cyclophosphamide is very effective in achieving high pCR rates and a significant reduction of Ki-67^[38].

MC alone or in combination with MTD chemotherapy is effective in achieving high pCR rates. Nevertheless, it is important to point out that all the studies mentioned above but one, incorporate platinum salts as a part of the neoadjuvant regimen; therefore, their results should be compared against regimens that contain neoadjuvant platinum as well. Interestingly, the only trial that did not include platinum salts, also achieved a higher pCR rate than standard MTD chemotherapy. In all cases, toxicity is of concern. The addition of granulocyte stimulating factor or the use of intermittent metronomic schedules might reduce toxicity while maintaining effectivity. We believe that this approach warrants consideration in the younger population, which is able to better tolerate toxicity and should be given the opportunity to achieve a better pCR and therefore better outcomes. Bigger phase III studies comparing MC vs MTD are needed.

ADJUVANT SETTING

Adjuvant chemotherapy in BC aims to eliminate minimal residual disease. The antiangiogenic and pro-immune properties of MC potentially induce tumor dormancy and eradicate residual cancer cells, becoming an option to improve outcomes in TNBC patients. Attempts to replace standard MTD chemotherapy with metronomic capecitabine have failed, resulting in inferior outcomes^[39]. Recently, intensifying adjuvant chemotherapy or adding maintenance with metronomic methotrexate, cyclophosphamide or capecitabine have been tested with promising results (Table 3).

Intensification of adjuvant chemotherapy

Nasr *et al.*^[40] reported data on a small phase III study that evaluated the role of metronomic methotrexate and cyclophosphamide after adjuvant therapy with anthracyclines, taxanes and carboplatin for stage II or III TNBC. One hundred fifty-eight patients were enrolled and randomized to 3 cycles of FEC-100 followed by 3 cycles of docetaxel and carboplatin followed by methotrexate and cyclophosphamide for 1 year or to 3 cycles of FEC-100 followed by 3 cycles of docetaxel without any further treatment. Although not starting from a standard of care due to the inclusion of carboplatin, this trial

showed important benefits in median DFS (28 mo vs 24 mo, $P = 0.05$) and OS (37 mo vs 29 mo, $P = 0.04$) with the addition of carboplatin plus metronomic maintenance in a head-to-head design^[40].

FinXX, a large randomized phase 3 clinical trial integrated capecitabine into standard adjuvant therapy. Women with axillary node-positive or greater than 20 mm node-negative BC of any histology were randomly assigned to receive either 3 cycles of docetaxel and capecitabine followed by 3 cycles of cyclophosphamide, epirubicin, and capecitabine ($n = 743$) or 3 cycles of docetaxel followed by 3 cycles of FEC ($n = 747$). The primary endpoint was recurrence-free survival (RFS), and it was not significantly different between the groups. However, in an exploratory analysis, adding capecitabine seemed to impact BC-specific survival (HR = 0.64; 95%CI: 0.44 to 0.95; $P = 0.027$) and RFS in women with TNBC, particularly those who had more than 3 metastatic axillary lymph nodes at the time of diagnosis^[41].

As currently proposed, adding metronomic chemotherapy to MTD adjuvant regimens hasn't improved outcomes in TNBC. Nevertheless, selected high-risk patients might derive some benefit that needs further exploration.

Maintenance-only approach

The phase III IBCSG Trial 22 enrolled 1086 women with triple negative or HER-2 positive BC with any nodal involvement. After adjuvant chemotherapy, patients were randomized to maintenance with continuous oral cyclophosphamide and weekly oral methotrexate for 1 year vs observation. After a median follow-up of 6.9 years, DFS was not significantly better for patients assigned to maintenance compared with those assigned to observation. Nevertheless, patients with TN, node-positive disease had a non-significant reduction of 7.9% in the absolute risk of relapse ($n = 340$; HR = 0.72; 95%CI: 0.49 to 1.05). In general, the metronomic part of the treatment was well tolerated with only 14% of patients experiencing a grade 3 or 4 treatment-related AE^[42].

A different approach was evaluated in the CREATE-X study, presented at the 2015 San Antonio Breast Cancer Symposium. This phase 3 randomized clinical trial evaluated the role of capecitabine maintenance in 910 HER2-negative (TN and luminal) BC patients with residual disease defined as no pCR or node-positive disease, after neoadjuvant chemotherapy with anthracycline and/or taxanes. Thirty-one percent of patients had TNBC, 80% received sequential anthracyclines and taxanes, and approximately 60% had prior 5-FU. Patients were randomized to receive capecitabine 2 wk on and 1 wk off, for up to 8 cycles vs observation. Only 38% and 58% of patients completed 8 and 6 cycles of chemotherapy respectively. At 5 years, DFS (primary endpoint) was 74.1% with capecitabine maintenance compared to 67.7% in the control arm,

Table 3 Adjuvant metronomic chemotherapy in triple negative breast cancer

	Ref.	Study design	n	Regimens	Characteristics	Outcome	Adverse events
MTD plus MC	Nars <i>et al</i> ^[40] 2015	Phase III	n: 158 A: 78	Arm A: Part 1 (3 cycles) Day 1 5FU 500 mg/m ² PO Day 1 E 100 mg/m ² Day 1 CTX 500 mg/m ² Day 1-2 MTX 2.5 mg twice/d PO Part 2 (3 cycles) Day 1 T 80 mg/m ² Day 1 Ca 5AUC Followed by MC × 1 yr Daily CTX 50 mg/d PO	Median age: 46 yr TNBC Stages II-III Tumor size > 1.0 cm Positive or negative axillary lymph nodes; ECOG < 2	Median DFS = 2 Arm A: 28 mo Arm B: 24 mo P = 0.05 OS : Arm A: 37 mo Arm B: 29 mo P = 0.04	Arm A Neutropenia G3: 19% Neutropenia G4: 1.9% Febrile neutropenia G3: 12% Nausea, vomiting G3: 12% Arm B: Neutropenia G3: 17% Febrile Neutropenia G3: 9%
	FIN XX <i>et al</i> ^[41] 2011	Phase III	A: 753	Arm A : Part 1 - every 3 wk for 3 cycles Day 1 T 60 mg/m ² IV Day 1-15 X 900 mg/m ² twice/d PO Followed Part 2 -every 3 wk for 3 cycles Day 1 CTX 600 mg/m ² IV	Median age: 52 yr Luminal, TNBC, Her2 T1: 46%, T2: 47% 1-3 positive axillary nodes: 62% > 3 positive axillary nodes: 28% Grade 3: 42% ER negative: 24%	DFS 5 yr (P = 0.087) A: 86.6% B: 84.1% Subgroup: TNBC > 3 axillary nodes: HR, 0.64; 95%CI: 0.44 to 0.95 (P = 0.027)	6 deaths related to treatment Arm A: 4 patients Arm B: 2 patients Discontinued treatment Arm A: 24% Arm B: 3%
			B: 747	Day 1 E 75 mg/m ² IV Day 1-15 X 900 mg/m ² twice/d PO Arm B: Part 1 (every 3 wk x 3 cycles) Day 1 T 80 mg/m ² IV Part 2 (every 3 wk x 3 cycles) Day 1 CTX 600 mg/m ² IV Day 1 E 75 mg/m ² IV Day 1 5FU 600 mg/m ² IV	Her 2 +: 19%		
Main-tenance	IBCSG Trial 22 Oct. 2016 ^[42]	Phase III	n: 1086 A: 542	Arm A: (every week for 1 yr) Daily CTX 50 mg/d PO Day 1-2 MTX 2.5 mg twice/d PO on	Median age: 51 yr TNBS, Her 2 Premenopausal: 45%	6.9 yr OS: HR 0.84; 95%CI, 0.66 to 1.06; P = 0.14); TNBC: (n = 814; HR = 0.80; 95%CI: 0.60 to 1.06)	Arm A Grade 3-4 treatment related AE: 14% patients Hypertransaminasemia G3 G4: 7%
			B: 539	Arm B: Observation	Her2 +: 19%, only 52% received trastuzumab TNBC: 75%	TNBC, node-positive disease: n = 340 HR = 0.72; (95%CI: 0.49 to 1.05)	Leukopenia G3-G4 : 2% 2 patients with AML
					Tumor > 2 cm: 54% Grade 3: 84% 1-3 node +: 25% > 3 node +: 16% Prior anthracycline: 60% Prior anthracycline + taxane: 26.1%		

CREATE-X trial 2015 ^[43]	Phase III	n: 455	Arm A: (every 3 wk for 8 cycles) Day 1-14 X 1250 mg/m ² twice/d Arm B: Observation	Luminal TBNC patients Prior: Neoadjuvant no pCR or node positive Anthracycline and/or taxane: 80% 5FU regimen: 60% Six cycles completed: 58% Eight cycles completed: 38%	5 yr DFS: (<i>P</i> = 0.00524). A: 74.1% B: 67.7% 30% reduction in risk 5 yr OS <i>P</i> < 0.01 A: 89.2% B: 83.9%	Arm A: HFS G3: 10.9%
Ongoing CIBOMA/2004-01/ GEICAM 2003-11 trial 2010 ^[45]	Phase III	A: 207 B: 193	Arm A: every 3 wk for 8 cycles Day 1-14 X 1000 mg/m ² per twice day PO Arm B: Observation	Median age: 51 yr TNBC Caucasian: 63.9% Postmenopausal: 68.2% Basal phenotype: 82% Neoadjuvant: 9.7% Adjuvant: 86.4% Complete 8 cycles: 77.3%	Ongoing	Arm A: HFS G3: 17.4% Diarrhea: 2.9% Fatigue: 1.9%
ECOG - ACRIN Cancer Research Group EA 1131 trial ^[46]	Phase III	Expected 562	Arm A: observation Arm B: Carboplatin / Cisplatin day 1 IV every 3 wk for 4 cycles Arm C: Capecitabine twice daily on days 1-14 every every 3 wk for 6 courses	TNBC Stage II - III Residual basal like disease after neoadjuvant chemotherapy	Ongoing	Ongoing

5FU: 5-Fluoracil; E: Epirubicin, Ca: Carboplatin; T: Docetaxel; CTX: Cyclophosphamide; MTX: Methotrexate; X: Capecitabine; AT: Anthracycline/taxane regimen; HFS: Hand-foot syndrome.

with a statistically significant 30% reduction in the risk of recurrence (one-sided *P* = 0.00524). Likewise, a statistically significant reduction in the risk of death was observed, with OS rates of 89.2% and 83.9%, respectively (one-sided *P* < 0.01)^[43]. In the subgroup analysis, the benefit of adding capecitabine was even greater in the TNBC subgroup which achieved a 42% reduction in the risk of recurrence^[43].

Despite the fact that both phase III trials evaluated maintenance therapy for early BC, there exist remarkable differences on their design and target population (Table 4). The IBCSG trial 22 included hormone negative-receptor early BC patients, of whom only 26% received current standard chemotherapy with anthracyclines and taxanes. Moreover, only 59% of the HER 2 positive patients received anti HER 2 target agents. The varying treatments logically modified outcomes with statistical implications. Also, because all patients were recruited after adjuvant therapy, no risk groups were identified. Treatment non-adherence was also an issue as the study had a high incidence (13%) of not-started treatment in those assigned to CM maintenance.

On the other hand, the CREATE-X study included luminal and TNBC patients, of whom 80% received sequential anthracyclines and taxanes. Outstandingly, this trial very early recognized residual disease as a poor prognostic factor and considered the addition of capecitabine as maintenance aiming to improve DFS and OS. This study included a better selected but still

heterogeneous population of luminal and TNBC patients. We believe that, as for luminal BC patients, pCR has not been correlated with outcomes, the positive results observed in both populations are produced by different mechanisms and mostly driven by the TNBC cases. A limitation of the CREATE-X study is the fact that these results were obtained in an only-Asian population, precluding their generalizability, particularly in terms of sensibility and tolerance which differs from those reported for the Caucasian population^[44].

Residual disease after neoadjuvant chemotherapy is a biomarker of high risk. In this setting, further treatment seems to be beneficial, especially for TNBC. We believe that selecting the population for clinical trials through this or other biomarkers is key for designing further research initiatives.

Ongoing trials and future perspectives

Ongoing trials are exploring the role of MC in different settings. The CIBOMA/2004-01/GEICAM 2003-11 trial, added capecitabine as maintenance after standard chemotherapy exclusively for TNBC. Patients were randomized to receive standard anthracycline and/or taxane-containing chemotherapy or 4 cycles of doxorubicin-cyclophosphamide (for node-negative disease) as (neo)adjuvant treatment followed by 8 cycles of capecitabine at 1000 mg/m² twice a day, 14 d on and 7 d off, every 3 wk vs observation. The most frequent grade 3/4 capecitabine-related clinical AE were hand-foot

Table 4 Maintenance for triple negative breast cancer

	IBCSG Trial 22, Oct. 2016	CREATE-X trial, 2015
Study design	Phase III	Phase III
Accrual time	2000-2012	2007-2012
Number of patients	N: 1086	N: 910
	CM: 542	X: 455
	Obs: 539	Obs: 455
Setting	Prior adjuvant ± RT	Prior neoadjuvant ± RT
Study population	TNBC: 75%	Luminal or TNBC
	HER2+: 19%	No pCR or node positive
Previous treatment	A + CMF: 60%	A: 4.1%
	CMF: 16%	AT sequential: 81%
	AT sequential + CMF: 26%	AT concurrently: 13.6%
	H: 59% (of HER2+)	TC: 5%
Study treatment	C 50 mg/d PO Daily M 2.5 mg bid PO Days 1-2 vs Observation	X 1250 mg/m ² twice/d PO Day 1-14 vs Observation
Time of treatment	Every week for 1 yr	Every 3 wk for 8 cycles (6 mo)
DFS	5 yr DFS:	5 yr DFS:
	CM: 78.1%	X: 74.1%
	Obs: 74%	Obs: 67.7%
	HR = 0.84 (95%CI: 0.66 to 1.06; P = 0.14)	HR (95%CI): 0.70 (0.53-0.93); P = 0.00524
	TNBC: n = 814; HR = 0.80; 95%CI: 0.60-1.06	30% reduction in risk
	TNBC, node-positive disease: n = 340; HR = 0.72; 95%CI: 0.49-1.05	
OS	No results	5 yr OS
		X: 89.2%
		Obs: 83.9%,
		P < 0.01
Adverse events	Hipertransaminasemia	X: HFS G3: 10.9%
	G3-G4: 7%	Neutropenia G3: 6.6%
	Leukopenia: 2%	Diarrhea G3: 3%
		Obs: Neutropenia 1.6%
		Diarrhea: 0.4%

C: Cyclophosphamide; M: Methotrexate; X: Capecitabine; ER: Estrogen receptor; PR: Progesterone receptor; A: Anthracycline; F: 5Fluoracil; T: Taxane; TNBC: Triple negative breast cancer; H: Herceptin.

syndrome (17.4%), diarrhea (2.9%), and fatigue (1.9%). After 6 years of follow-up and with a small number of events, no differences in DFS have been detected so far. Disease-free survival (DFS) is still ongoing^[45].

The phase III ECOG-ACRIN Cancer Research Group - EA 1131 trial will define which treatment-if any- is more effective in prolonging DFS in patients with residual basal-like TNBC, following neoadjuvant chemotherapy. Five hundred sixty-two patients are expected to be included and randomized to receive further treatment with cisplatin/carboplatin, capecitabine or observation. This clinical trial is currently recruiting participants. The estimated primary completion date is on May 2019^[46].

CONCLUSION

MC is a multi-mechanism therapy that due to its accessibility and affordability, stands as an attractive alternative or complement for a selected group of TNBC patients in both the neoadjuvant and adjuvant setting. In neoadjuvant regimens pCR rates obtained with MC are high, as well as it is toxicity. In the adjuvant setting, metronomic maintenance for patients with residual disease after neoadjuvant therapy seems to be feasible and effective in prolonging DFS and these results are encouraging.

Considering the dismal prognosis of TNBC, any

strategy that potentially improves outcomes, specially being the oral agents broadly available and inexpensive, should be considered and certainly warrants further exploration. Finally, the benefit of MC needs to be validated in properly designed clinical trials where the selection of the population is the key.

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With increasing trends of prostate cancer in the Saudi Arabia and Arab World: Should we start screening programs?

Mostafa A Arafa, Danny M Rabah

Mostafa A Arafa, Danny M Rabah, Cancer Research Chair, College of Medicine, King Saud University, Riyadh 4536, Saudi Arabia

Danny M Rabah, Department of Surgery, College of Medicine, King Saud University, Riyadh 4536, Saudi Arabia

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Correspondence to: Mostafa A Arafa, MD, Professor of Epidemiology, Cancer Research Chair, College of Medicine, King Saud University, 3125 King Abdullah street, Riyadh 4536, Saudi Arabia. marafa@ksu.edu.sa
Telephone: +966-5-8129051

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Abstract

Incidence rate for prostate cancer in the Arab World

is significantly lower than United States and Europe, it ranges from 5.5% to 39.2%. However, the incidence and the number of deaths is expected to increase. In Saudi Arabia, the crude incidence rate and age standardized incidence rate of prostate cancer are reported to be steadily increasing in between 2001-2008. Only two screening trials were attempted in 2001 and 2009 which yielded an incidence rate of 1.17% and 2.5% respectively. Men in the Arab world are sharing a common characteristic of poor knowledge and poor attitude towards prostate cancer examination and screening practices. They are ill-informed about the PSA test's strengths and drawbacks because the doctors are not talking to them about the importance of counselling. Men should be encouraged to do PSA testing before the age of 50 and till the age of 70 years. This could be achieved by enhancing their attitude and enriching the knowledge of the physicians towards PSA testing, harms and benefits, through shared decision making, which would increase men's knowledge scores, reduced their decisional conflict and promote greater involvement in decision making.

Key words: Prostate cancer; Incidence; Arab World; Screening

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Core tip: Despite the very low incidence and the number of deaths from prostate cancer in the Arab World, it is expected to increase. In Saudi Arabia, the crude incidence rate and age standardized incidence rate of prostate cancer are reported to be steadily increasing in between 2001-2008. Men in the Arab world are characterized by poor knowledge and poor attitude towards prostate cancer examination and screening practices. We recommend against mass screening, but men should be encouraged to do PSA testing before the age of 50 and till the age of 70 years, through shared decision making.

Arafa MA, Rabah DM. With increasing trends of prostate cancer in the Saudi Arabia and Arab World: Should we start screening programs? *World J Clin Oncol* 2017; 8(6): 447-449 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v8/i6/447.htm> DOI: <http://dx.doi.org/10.5306/wjco.v8.i6.447>

INTRODUCTION

Prostate cancer is representing a major public health problem in the developed world, the figures reported from Europe and United States indicated a higher age standardized incidence rate (ASIR) and mortality rate. The incidence varies more than 25-fold worldwide, where the rates are higher in Northern American, Australia, and northern Europe, because of the practice of PSA testing and biopsy which has become widespread in those areas. The reported mortality rates paralleled the incidence rates, with a considerable decrease in most of the countries except Eastern Europe^[1,2].

The corresponding reported figures from the Arab World is much and significantly lower. The ASIR rate ranged from 39.2% in Lebanon to 5.5% in Saudi Arabia, while the data on mortality rates are not available^[3] (Figure 1).

Access to the health care and accuracy of the cancer registries in the Middle East is affecting the ASIR of prostate cancer reported from such countries. However, GLOBOCAN, 2012 reported that prostate cancer incidence in the Middle East North Africa (MENA) region is expected to increase from 29377 new cases in 2012 to 38562 new prostate cancer cases in 2020 along with an increase in mortality from prostate cancer from 15422 prostate cancer deaths in 2012 to 19681 deaths in 2020^[1]. In Saudi Arabia, the crude incidence rate and ASIR of prostate cancer are reported to be steadily increasing in between 2001-2008 and then after^[4].

No screening programs were adopted in the Arab world except for breast cancer. The first screening trial for prostate cancer was attempted in Saudi Arabia in 2001 and yielded an incidence of 1.17%^[5]. Nine years later Rabah reported an incidence of 2.5%, in a larger sample and in a different health facility, amongst the studied cohort; and 27% were metastatic^[6]. In Saudi Arabia, Many confirmed cases of prostate cancer were diagnosed before the age of 50, in addition, the distribution of the PSA levels among the Saudi men was lower than other European countries^[7].

The men in the Arab world are sharing a common characteristic of poor knowledge and poor attitude towards prostate cancer examination and screening practices^[8]. Such poor behavior towards their health could be ascribed to their level of awareness, or different barriers which may prevent them from seeking early detection and diagnosis of prostate cancer, *i.e.*, mistrust of physicians, fear of diagnosis, fear of testing procedures, DRE threatens sexuality and others^[9].

The men in the Arab world remain ill-informed about

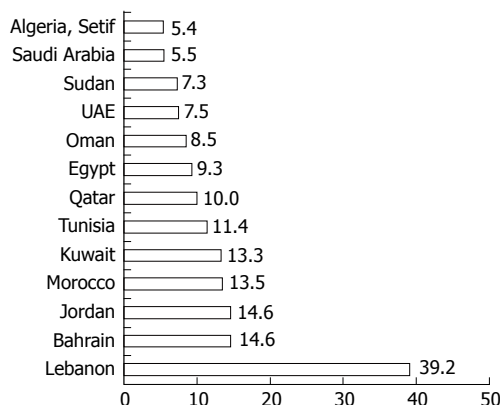


Figure 1 Age standardized incidence rate (%) of prostate cancer in the Arab World during the period 2010-2014.

the PSA test's strengths and drawbacks because the doctors are not talking to them about the importance of counseling. The results of a survey on the primary health care physicians in Saudi Arabia about their knowledge and behavior on prostate cancer counseling and screening indicated that nearly 55% were practicing counseling and they had a poor attitude and deficient knowledge towards counseling and referring patients^[10]. The decision to provide screening would be influenced by factors related to the physicians, patients and screening guideline. Physicians who have good scientific evidence are more likely to practice informed decision making with their patients as they believe that men need to know about the Pros and Cons of PSA testing to make their decisions^[10].

A recent review concluded that the evidence does not indicate that the benefits of using PSA for prostate cancer screening outweigh the harms^[11]. In the same context, in our Arab countries, the incidence of prostate cancer is still low, but the trend is increasing in the last few years, however, we recommend against mass screening, but encourage men to do PSA testing before the age of 50 and till the age of 70 years. This could be achieved by enhancing their attitude and enriching the knowledge of physicians towards PSA testing, harms and benefits, through shared decision making, which would increase men's knowledge scores, reduced their decisional conflict and promote greater involvement in decision making.

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