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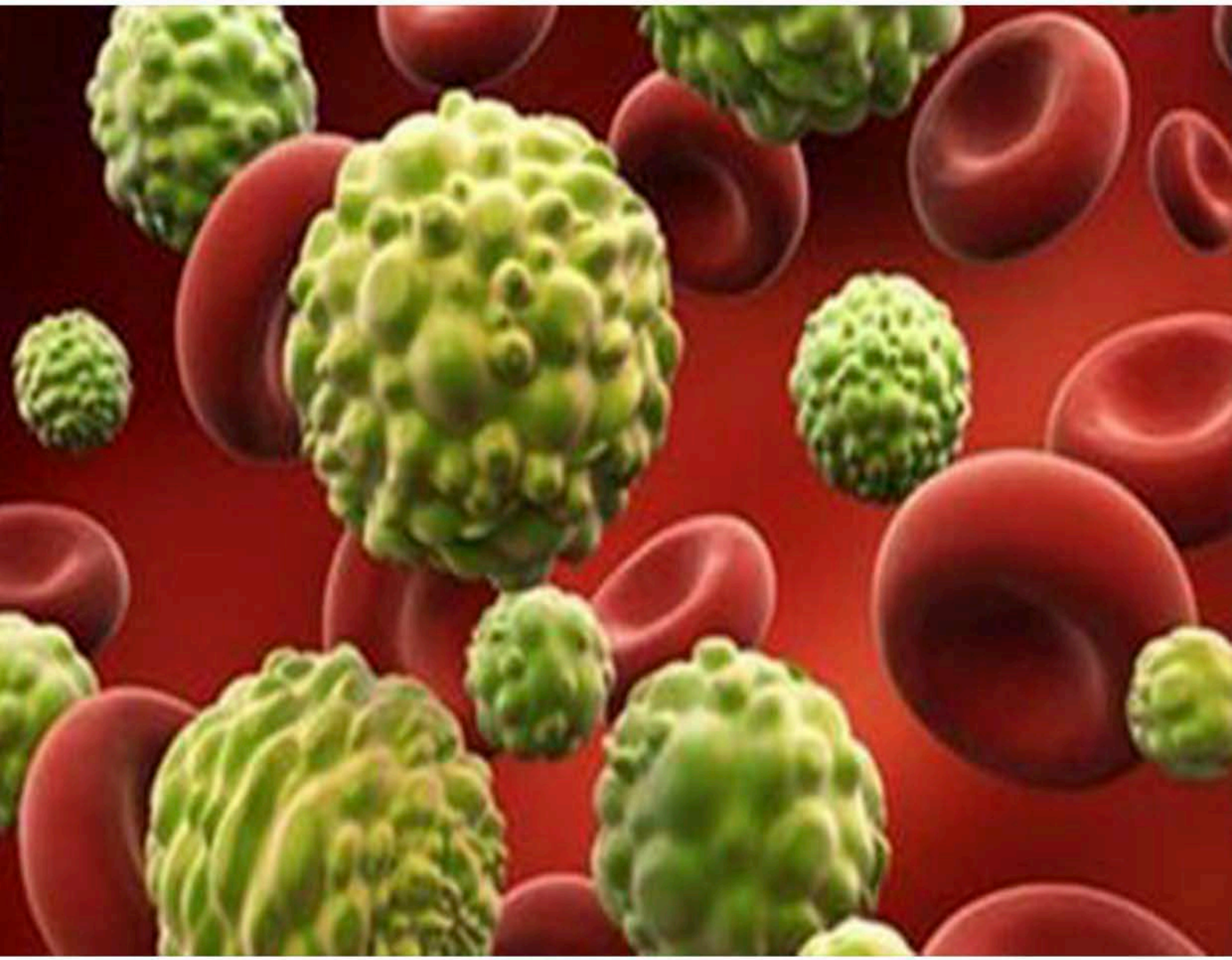

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Current Cancer Reports

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Current Cancer Reports

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EDITORIAL

Cancer, Mankind's Challenge

Editor-in-Chief: Ying-Yu Cui[1,2,3,4]

Cancer, or malignant tumour, is a group of diseases defined by the uncontrollable growth of the transformed cells, and their capabilities of invasion into surrounding healthy tissues and metastasis to remote sites in the body of organisms[1,2]. According to different origins, it can be further divided into five subtypes: carcinoma, adenocarcinoma, sarcoma, lymphoma/leukemia and myeloma. Cancer is the second leading cause of death worldwide after cardiovascular disease (GBD 2013 Mortality and Causes of Death Collaborators 2015)[3]. Usually, scientists attribute tumorigenesis to the control loss of cell proliferation, inhibition of cell differentiation and blockade of cell senescence and death at cellular level; chromosome aneuploidy[4,5] and hyperactive telomerase[6] at sub-cellular level; excessive activation of oncogenes and excessive inhibition of anti-oncogenes, gene mutation and epigenetic modification (DNA methylation and histone acetylation, *etc*.)[7] at molecular level, respectively. Mutagens in *in vitro* environment, including physical carcinogens (UV, X-rays, *etc*.), chemical carcinogens (Benzopyrene, Aflatoxin B1, *etc*.) and biological carcinogens (DNA viruses, RNA retroviruses) can promote the transformation of benign tumours to malignant tumours with the help of factors in *in vivo* environment (*e.g.* hormone secretion disorder[8], immune dysfunction[9], chronic inflammation[10,11] and excessive oxygen radicals[12]). Recent years, the relationships between various viruses, bacteria and malignant tumours have aroused concerns of cancer researchers, e.g. Human papillomavirus (HPV) & cervical cancer, head and neck cancer, Hepatitis B/C virus (HBV, HCV) & liver cancer, Epstein-Barr virus (EBV) & various lymphoma and nasopharyngeal carcinoma, Human T-cell lymphotropic virus type-1 (HTLV-1) & adult T-cell leukemia (ATL), Human immunodeficiency virus (HIV) & lymphoma, Human herpesvirus 8 (HHV-8) & kaposi sarcoma, Helicobacter pylori (HP) & gastric cancer, and Porphyomonas gingivalis (PG) & esophageal cancer, *etc*. All these indicate a complex relationship between viruses, bacteria, malignant tumours and immunity.

Genetically, carcinogenesis usually results from DNA point mutations and alterations of larger amounts of DNA (including chromosome translocation, inversion, duplication/deletion and aneuploidy, *etc*.)[13,14], not only because all these changes can possibly lead to gene amplification and/ or loss of heterozygosity (LOH) of tumour suppressor genes (anti-oncogenes)[15], but also bring about overexpression of oncoproteins, further activate the signalling pathway to carcinogenesis.

"Is cancer inherited?" is another topic of general public concern, because there is a high incidence of certain cancers in some places, and presenting a familial character. For example, nasopharyngeal carcinoma is highly prevalent in

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Guangzhou, Dongguan and Zhanjiang, Guangdong province; hepatocellular carcinoma prevalent in Qidong, Jiangsu Province; and laryngeal cancer prevalent in Linzhou, Henan Province, *etc*. in China. Usually, most geneticists believe that tumours and cancers originate from malignant transformation of somatic cells and are rooted in gene mutations. And cancer is just genic disease instead of genetic disease. Cancer shows familial characteristics in some areas just because cancer susceptibility genes[16,17] can be transmitted in the family and their mutations make cancers seem inheritable in the same living environment. Therefore, isolation and identification of candidate tumour or cancer susceptibility genes are also worthwhile to explore and report.

It is not possible to overstate cancer is the fatal disease human being have to face at present, because it is very hard for the detection and diagnosis of cancer at early stage in clinic. Once diagnosed, it is in the middle and late stages. Protein biomarker (e.g. alpha fetoprotein AFP, carcinoembryonic antigen CEA, *etc*.) detection, imaging techniques and tissue biopsy are successively and widely used to detect and diagnose cancer in clinic, however, these methods still fail to detect early cancerous cells on account of sensitivity deficiency, false negative or even false positive. Recently, oncogene expression pattern detection at RNA level seems ready to come out at one's call[18]. More optimal biomarkers for tumour or cancer diagnosis need exploring and developing for early genetic test of cancer.

At present, surgery, radiation therapy, chemotherapy, Chinese medicine treatment and targeted therapy are the major methods for cancer treatment in clinic. However, none of these methods can cure cancer fundamentally. Surgery may increase the risk of cancer cell invasion and metastasis; radiotherapy and chemotherapy not only kill cancer cells, but also damage normal cells; Chinese medicine treatment cure symptoms instead of root causes; and targeted therapy is so expensive that common civilians cannot afford it. In addition, resistance to chemotherapeutic drugs is currently a major problem in cancer therapy, accounting for treatment failure in over 90% of human patients with metastatic or recurrent cancer[19]. In response to this situation, some scientists put forward hypothesis that cancer consists of a larger number of cancer cells and a few of cancer stem cells[20,21], the former with the characteristics of uncontrollable proliferation and metastasis, and the latter with ATP-binding cassette transporters to remove drugs from the cells[22], further lead to the resistance to anti-cancer drugs. All these remind us that we can screen anti-cancer drugs from natural products targeting the signalling pathways controlling proliferation, metastasis and invasion of cancer cells[23–28], and targeting ATP-binding cassette transporters[22] of cancer stem cells, respectively. Recent years, new strategies for cancer treatment have been proposed and developed, including starvation of cancer cells by inhibiting angiogenesis[29,30], gene therapy, immunotherapy via chimeric antigen receptor- T cell (CAR-T)[31] and integrated Chinese and Western medicine therapy[32], *etc*. A good case in point is the 2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation (via CTLA-4)[33,34]. Despite the potential limitations of immunotherapy[35], its novel development may bring hope to the treatment of malignant tumours in the future[36].

Considering the heterogeneity of tumour[37,38] and multiple stages of carcinogenesis[39,40], even patients with the same cancer have different therapeutic effects on the same anticancer drug, and precision medicine was put forward to satisfy the needs of personalized therapy of patients with the same disease (e.g. cancer)[41]. However, as far as current technological progress is concerned, there is still a long way to go.

Just as every coin has two sides, cancer is also thought a normal form of life by some scientists, not only because cancer cell surely exists in nearly everybody of human, but also cancer patients who have a 5-year survival rate after surgery are usually considered to be cured in clinic. What's more, there is no shortage of cancer-bearing survivors to old age and death. In other words, under physiological homeostasis, everyone can live with the transformed cells, just when appropriate and necessary, the cells can be removed by apoptosis and phagocytosis without any side effects (e.g. inflammation) in human body. Once their surroundings (microenvironments) deteriorated, the balance broken, the transformed cell growth and proliferation will predominate over its surrounding somatic cells, gradually through hyperplasia, dysplasia, tumour in situ, and metastatic tumour stages finally develop into malignant tumours, or cancers. Recently, tumour angiogenesis, cancer invasion, metastasis and cancer interaction with its surroundings (microenvironments)[42,43] have become hot spots in the fields of cancer research. Therefore, all factors that lead to microenvironment deterioration, including abnormal lifestyles (e.g. smoking, alcoholism, high-fat, and high-salt diet, *etc*.) and irregular way of working & sleeping (e.g. long-term overnight work, sedentariness & less movement, and bad mental condition, *etc*.), should arouse people's attention. In one word, cancer has become the common challenge of mankind, needing us to work together in the same boat, concentrate and defeat it in the coming future.

Current cancer reports (CCR) (ISSN: 2661-3166) is a new born academic journal, a platform aiming to provide doctors, researchers, physicians, pharmacists and healthcare professionals all over the world to communicate their latest research progress,[44,45] novel ideas[46], technique innovations[47–49] and candidate anti-cancer drug leads[50] in the fields of cancer-related research, prevention and treatment. As we know, the first year of a newborn is always a challenge, as it was the case with a journal. Sincerely wish you and your colleagues to submit manuscripts of high quality and support her growth. Let's witness her healthy growth with the process of human conquering cancer together.

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REVIEW

A review of home-based physical activity interventions for breast cancer survivors

Steven S. Coughlin[1,2*] Lee Caplan[3] Rebecca Stone[2] Jessica Stewart[4]

Abstract: As breast cancer relative survival continues to increase, many breast cancer patients face many issues, including recurrence of cancer and cancer-related side effects that impact several aspects of their quality of life. With breast cancer patients living longer, there is more of a concern for negative breast cancer outcomes. Although physical activity is an affordable and relatively convenient way to improve breast cancer outcomes, only about one-third of breast cancer survivors engage in the recommended level of physical activity. This article reviews articles published to date to examine whether home-based physical activity interventions are effective in improving physical activity and other outcomes among breast cancer survivors who have completed primary therapy for the disease. The present review is based upon bibliographic searches in PubMed and CINAHL and relevant search terms. Articles published in English from 1980 through February 28, 2019 were identified. A total of 360 article citations were identified in PubMed and non-duplicates in CINAHL. After screening the abstracts or full texts of these articles and reviewing the references of previous review articles, 20 studies that met the eligibility criteria. Three of the studies were pre-/post-test trials and 17 were randomized controlled trials. Home-based exercise programs are effective in improving physical activity among breast cancer survivors who have completed primary therapy for the disease. Home-based exercise programs such as walking programs offer a convenient and affordable option for women who wish to increase their physical activity and maintain a healthy lifestyle.

Keywords: breast cancer survivors, physical activity, women

1 Introduction

The five-year relative breast cancer survival rate in the US continues to increase and is now about 91%[1]. As the rate increases, many breast cancer patients face many issues, including recurrence of cancer and cancer-related side effects that impact several aspects of their quality of life[2]. To reduce risk of cancer recurrence, the American Institute for Cancer Research also recommends that cancer survivors meet physical activity guidelines (AICR)[3]. Of women diagnosed with breast cancer, 50–96% experience weight gain during treatment[4]. This weight gain after diagnosis usually ranges between 2.5 and 6.2 kg (5.5 to 13.6 lbs)[5]. Among breast cancer survivors (BCSs), physical activity improves physical functioning, cardiovascular fitness, emotional well-being, and psychological adjustment, while lowering fatigue, depression, and anxiety, and helping to maintain a healthy body weight[6]. In addition, studies suggest that the immunological status of breast cancer patients improves after physical activity[7]. However, levels of physical activity in this population are low.

Physical inactivity and excessive weight gain that can occur following breast cancer treatment increases the risk of breast cancer recurrence, other chronic diseases, and all-cause and breast cancer-related mortality[8]. Physical inactivity increases the risk of obesity, which increases circulating estrogen levels and mortality. Exercise can lower circulating levels of estrogen and potentially reduce tumor proliferation. Although physical activity is an affordable and relatively convenient way to improve breast cancer outcomes, only about one-third of breast cancer survivors engage in the recommended level of physical activity[9].

Home-based exercise programs, including walking programs, offer a convenient and affordable option for women who wish to increase their physical activity and maintain a healthy lifestyle. This manuscript reviews ar-

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ticles published to date to examine whether home-based physical activity interventions are effective in increasing physical activity and improving other outcomes among breast cancer survivors who have completed primary therapy for the disease (adjuvant chemotherapy, radiation, or surgery).

2 Methods

The present review is based upon bibliographic searches in PubMed and CINAHL (Cummulative Index to Nursing and Allied Health Literature) and relevant search terms. Articles published in English from 1980 through February 28, 2019 were identified using the following MeSH (Medical Subject Heading) search terms and Boolean algebra commands: home based AND physical activity AND breast cancer. The following MeSH search terms and Boolean algebra commands were also used: walking intervention AND breast cancer. The searches were not limited to words appearing in the title of an article nor to studies in a particular country or geographic region of the world. The references of review articles were also reviewed (Bluethman *et al*. 2015; Paxton *et al*. 2019). Information obtained from bibliographic searches (title and topic of article, information in abstract, study design, and key words) was used to determine whether or not to retain each identified article. Only studies written in English that examined the impact of breast cancer survivorship care plans on health outcomes were eligible for inclusion.

3 Results

A total of 360 article citations were identified in PubMed and non-duplicates in CINAHL (Figure 1). After screening the abstracts or full texts of these articles and reviewing the references of previous review articles, we were left with 20 studies that met the eligibility criteria. Three of the studies were pre-/post-test trials, and 17 were randomized controlled trials.

Pinto *et al*.[10] conducted a 12-week randomized controlled trial of physical activity counseling delivered via telephone, combined with weekly exercise tip sheets (Table 1). Eighty-six women who had completed therapy for stage 0-II breast cancer were enrolled in the trial. The physical activity group reported significantly more total minutes of physical activity and more minutes of moderate-intensity physical activity than the control group (p = 0.001).

In an eight-week pre/post-test trial of a community intervention that combined the use of pedometers with scheduling, goal setting, and self-assessment, Wilson *et al*.[11] found that the intervention led to significant increases in steps walked per day and improved attitude toward exercise, as well as significant decreases in body mass index and other anthropometric measures. Twenty-four African American breast cancer survivors were enrolled in the trial.

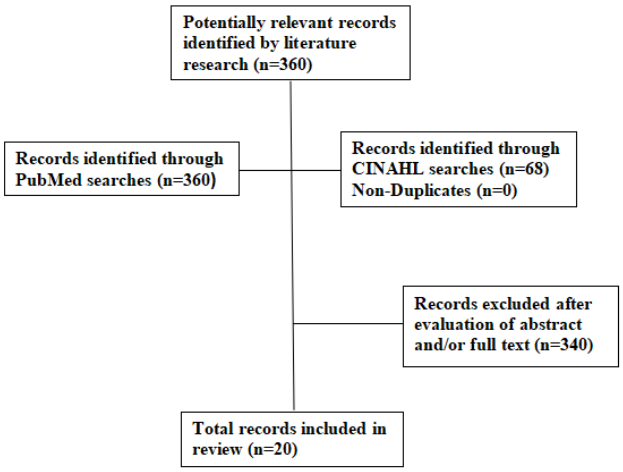

Figure 1. Flowchart of record selection process

Vallance *et al*.[12] conducted a 12-week randomized controlled trial with four arms: i) standard public health recommendation for physical activity; ii) breast cancer-specific physical activity print materials; iii) use of a step pedometer; or iv) a combination of print materials and use of a step pedometer. Physical activity increased by three minutes/week in the standard recommendation group compared with 70 minutes/week in the print material group (p = 0.117), 89 minutes/week in the pedometer group (p = 0.017), and 87 minutes/week in the combined group (p = 0.022). For brisk walking, all three intervention groups reported significantly greater increases than the standard recommendation group. The combined group also reported significantly improved quality-of-life (p = 0.003) and reduced fatigue (p = 0.052).

In a 12-week randomized controlled trial of a home-based walking intervention, Matthews *et al*.[13] found that intervention participants reported a significantly greater increase in walking for exercise than the controls (p = 0.01). In a 12-week randomized controlled trial of two home-based exercise programs (aerobic exercise, resistance training), Yuen and Sword[14] found a significant reduction in fatigue among participants in the aerobic exercise group compared with the resistance exercise group (p = 0.006). In addition, there was a significant improvement in the distance walked during a 6-minute walk test in the resistance exercise group (p = 0.009).

Payne *et al*.[15] conducted a randomized controlled trial of a home-based walking program among 20 women receiving hormonal therapy for breast cancer. There was

Table 1. Studies of home-based physical activity interventions for breast cancer survivors

Author	Design	Outcomes	Sample Size	Results
Pinto et al., 2005	12-week randomized controlled trial of physical activity counseling delivered via telephone, combined with weekly exercise tip sheets	Self-reported minutes of physical activity	86 women who had completed therapy for stage 0-II breast cancer	The physical activity group reported significantly more total minutes of physical activity and more minutes of moderate-intensity physical activity (p=0.001)
Wilson et al., 2005	8-week pre-/ post-test trial of a community intervention using pedometers with scheduling, goal setting, and self-assessment	Steps walked per day, body mass index, and attitudes	24 African American breast cancer survivors	Significant increases in steps walked per day and attitude toward exercise were reported, as well as significant decreases in body mass index and other anthropometric measures
Vallance et al., 2007	12-week randomized controlled trial with 4 arms: standard public health recommendation for physical activity; breast cancer-specific physical activity print materials; a step pedometer; or a combination of print materials and step pedometers	Self-reported moderate/vigorous physical activity minutes per week. Secondary outcomes were quality-of-life, fatigue, self-reported brisk walking, and objective step counts	377 women who had completed therapy for stage I-IIIa breast cancer	Physical activity increased by 3- minutes/week in the standard recommendation group compared with 70 minutes/week in the print material group (p=0.117, 89 minutes/week in the pedometer group (p=0.017), and 87 minutes/week in the combined group (p=0.022). For brisk walking, all three intervention groups reported significantly greater increases than the standard recommendation group. The combined group also reported significantly improved quality-of-life (p=0.003) and reduced fatigue (p=0.052).
Matthews et al., 2007	12-week randomized controlled trial of a home-based walking intervention	Self-reported physical activity	36 breast cancer survivors	Intervention participants reported a significantly greater increase in walking for exercise (p=0.01)
Yuen & Sword, 2007	12-week randomized controlled trial of two home-based exercise programs (aerobic exercise, resistance training)	Fatigue, functional capacity (6-minute walk test)		There was a significant reduction in fatigue among participants in the aerobic exercise group (p=0.006). There was a significant improvement in the distance of the 6-minute walk test in the resistance exercise group (p=0.009)
Payne et al., 2008	Randomized control trial of a home-based walking program	Fatigue, sleep disturbances, depressive symptoms, and biomarkers (cortisol, serotonin, interleukin-6, bilirubin)	20 women receiving hormonal therapy for breast cancer	There was a significant improvement in sleep scores in the intervention group compared with the control group (p=0.007). Serotonin levels were also significantly different between groups (p=0.009)
Yang et al., 2010	12-week randomized controlled trial of a home-based walking program	Symptom severity score and mood disturbance	40 breast cancer patients (stage I-IIIa) receiving an aromatase inhibitor	Women in the exercise group reported significantly lower symptom severity scores (p<0.01) and mood disturbance (p=0.02) compared with those in the control group
Kim et al. 2011	12-week randomized controlled trial of a home-based stage-matched exercise and diet intervention (telephone counseling and a workbook	Stage of motivational readiness for exercise and diet, physical activity, diet quality, quality-of-life, fatigue, anxiety, depression	45 breast cancer survivors, stage 0-III	The intervention group showed significantly greater improvement in motivational readiness for exercise (p<0.006) and diet (p<0.001), emotional functioning (p=004), fatigue (p=0.001), and depression (p=0.035)
Hatchett et al., 2013	12-week randomized controlled trial of an email physical activity intervention	Self-reported physical activity	74 breast cancer survivors	Significant differences in levels of physical activity were observed between groups at 6 (p=0.001) and 12 weeks (p<0.001)
Spector et al., 2014	Pre-/post-test trial of a home-based aerobic and resistance training exercise intervention (motivational interviewing and weekly telephone calls)	Self-reported and objectively assessed physical activity, quality-of-life, and fatigue	17 African American women who had completed therapy for stage 0-IIIa breast cancer, who were currently sedentary	There was a significant increase in total minutes of weekly physical activity (p=0.001). Total quality-of-life and fatigue scores improved, but neither was significant.
Denysschen et al., 2014	8-week pre-/ post-test trial of a home-based exercise program (resistance exercises and self-selected aerobic exercise)	Anthropometry and functional performance and cardiovascular endurance (3-minute step test)	26 breast cancer patients receiving an aromatase inhibitor	Participants reported a significantly lower number of painful joints, and improved quality-of-life (p<0.05). Significant improvements in grip strength (p<0.01), biceps curl (p<0.01), and sit-to-stand were also observed. There were no significant differences in anthropometric measures or cardiovascular endurance.
Baruth et al., 2015	12-week randomized controlled trial of a home-based walking program	Self-reported fatigue, quality-of-life, and walking	32 women who were early stage breast cancer survivors	Participants in the intervention group had improvements in fatigue and quality of life outcomes. Changes in fatigue and quality of life were associated with changes in walking behavior
Lahart et al., 2016	6-month randomized controlled trial of a physical activity intervention (face-to-face and telephone physical activity counseling)	Physical activity (primary outcome) and body mass, body mass index, body fat , health-related quality-of-life, insulin resistance, and lipids	80 post-adjuvant therapy breast cancer patients	Total, leisure and vigorous physical activity significantly increased in the intervention group compared to usual care group (p= 0.24, p=0.01, and p=0.007, respectively). Both body mass and body mass index decreased significantly in the intervention group compared to usual care group (p=0.04 and p=0.02, respectively). Total cholesterol and LDL-cholesterol decreased significantly in the intervention group compared to usual care group (p=0.001 and p=0.23, respectively).
Knobf et al., 2016	12-month randomized controlled trial of a aerobic-resistance exercise intervention compared to a home-based physical activity intervention	Bone mineral density and biomarkers of bone turnover	154 early postmenopausal breast cancer survivors	No significant difference in bone mineral density was observed between the two groups
Nyrop et al., 2017	6-week randomized controlled trial of a home-based walking program	Self-reported joint symptoms and psychosocial measures	62 post-menopausal women diagnosed with stage 0-III breast cancer, with aromatase inhibitor-associated arthralgia	Intervention group participants reported significantly increased walking minutes per week, reduced stiffness, less difficulty with activities of daily living, and less perceived helplessness in managing joint symptoms
Valle et al., 2017	3-arm, 6-month randomized controlled trial of a physical activity intervention (activity tracker and tailored feedback based on objective weight; tailored feedback alone; or control)	Change in weight	35 African American breast cancer survivors, stage I-IIIa	Median weight change was -0.9 in the intervention group that included activity trackers vs. 0.2% gain in the control group
Westphal et al., 2018	48-week multi-center randomized controlled trial of counseling and unsupervised exercise training vs. supervised physical training (24 weeks) followed by unsupervised training (additional 24 weeks). The supervised training was comprised of 45 minutes of stationary cycling and 30 minutes of resistance training twice a week.	Maximum power output on a cycle ergometer after 24 weeks of exercise	42 early-stage breast cancer patients receiving aromatase inhibitor treatment	After 24 weeks, the supervised arm achieved a significantly higher maximum output in watt (mean 132 +/- SD 34, 95% CI 117-147) compared to baseline 107 +/-25, 95% CI 97-117, p=0.012) with a higher output than the unsupervised arm (115 +/- 25, 95% CI 105-125, P=0.059).
Hirschey et al., 2018	Randomized controlled trial of a home-based physical activity intervention (a booklet about physical activity for breast cancer survivors, that included narrative messages and writing and thinking exercises)	Multidimensional exercise outcome measure	60 breast cancer survivors, stage Ia-IIb	Subjective exercise (weekly minutes) increased 2 minutes, and objective exercise increased by 970 steps, every 4 weeks in the intervention group compared to the control group (p=0.2676 and p=0.0283, respectively)
Bail et al., 2018	12-month randomized controlled trial of a home-based mentored vegetable gardening intervention	Vegetable consumption, physical activity, performance and function, anthropometrics, biomarkers, quality-of-life	82 breast cancer survivors, stage 0-III	Compared with the controls, intervention participants reported significantly greater improvements in moderate physical activity and demonstrated improvements in the 2-minute step test and arm curl (p-values<0.05).
Lahart et al., 2018	6-month randomized controlled trial of a home-based physical activity intervention	Cardiorespiratory fitness and physical activity	32 breast cancer survivors who had completed adjuvant therapy	Magnitude-based inference analyses revealed at least small beneficial effects on absolute and relative $\dot{V}O_2$ max (cardiorespiratory fitness), and total and moderate physical activity in the intervention compared to the usual care group.

a significant improvement in sleep scores in the intervention group compared with the control group (p = 0.007). Serotonin levels were also significantly different between groups (p = 0.009).

Yang *et al.*[16] conducted a 12-week randomized controlled trial of a home-based walking program among 40 breast cancer patients who were receiving an aromatase inhibitor. Women in the exercise group reported significantly lower symptom severity scores ($p<0.01$) and mood disturbance (p = 0.02) compared with those in the control group.

In a 12-week randomized controlled trial of a home-based, stage-matched, exercise and diet intervention (telephone counseling and a workbook), Kim *et al.*[17] found that the intervention group showed significantly greater improvement in emotional functioning (p = 0.04), and motivational readiness for exercise ($p<0.006$) and dieting ($p<0.001$), and reduced fatigue (p = 0.001) and depression (p = 0.035) than the controls.

In a 12-week randomized controlled trial of an email physical activity intervention, Hatchett *et al.*[18] observed significantly higher levels of physical activity in the intervention group at six (p = 0.001) and 12 weeks ($p<0.001$) compared to the controls.

Spector *et al.*[19] conducted a pre/post-test trial of a home-based aerobic and resistance training exercise intervention. The intervention included motivational interviewing and weekly telephone calls. They found a significant increase in total minutes of weekly physical activity (p = 0.001). Total quality-of-life and fatigue scores improved, but neither improvement was statistically significant.

Denysschen *et al.*[20] conducted an eight-week pre/post-test trial of a home-based exercise program (resistance exercises and self-selected aerobic exercise) among 26 breast cancer patients who were receiving an aromatase inhibitor. The participants reported a significantly lower number of painful joints and significantly improved quality-of-life ($p<0.05$). Significant improvements in grip strength ($p<0.01$), biceps curl ($p<0.01$), and sit-to-stand were also observed. There were no significant differences in anthropometric measures or cardiovascular endurance.

In a 12-week randomized controlled trial of a home-based walking program among 32 early-stage breast cancer survivors, Baruth *et al.*[21] found that participants in the intervention group had reduced fatigue and improvement in other quality of life outcomes.

Lahart *et al.*[22] conducted a six-month randomized controlled trial of a physical activity intervention (face-to-face and telephone physical activity counseling) among 80 breast cancer survivors. Total, leisure, and vigorous physical activity increased in the intervention group compared to the usual care group (p = 0.24, p = 0.01, and p = 0.007, respectively). Both body mass and body mass index decreased significantly in the intervention group compared to the usual care group (p = 0.04 and p = 0.02, respectively). In addition, total cholesterol and LDL-cholesterol decreased significantly in the intervention group (p = 0.001) but not in the usual care group (p = 0.23).

Knobf *et al.*[23] conducted a 12-month randomized controlled trial of an aerobic-resistance exercise intervention compared to a home-based physical activity intervention among 154 early postmenopausal breast cancer survivors. The outcomes of interest were bone mineral density and biomarkers of bone turnover. No significant difference in bone mineral density was observed between the two groups.

Nyrop *et al.*[24] conducted a six-week randomized controlled trial of a home-based walking program among 62 post-menopausal breast cancer patients with aromatase inhibitor-associated arthralgia. Intervention group participants reported significantly increased walking minutes per week, reduced stiffness, less difficulty with activities of daily living, and less perceived helplessness in managing joint symptoms compared to the controls.

Valle *et al.*[25] conducted a two-arm, six-month randomized controlled trial of a physical activity intervention (activity tracker and tailored feedback based on objective weight; tailored feedback alone; or control). The outcome of interest was change in weight. Thirty-five African American breast cancer survivors participated in the trial. Median weight change was -0.9% in the intervention group that included activity trackers vs. 0.2% gain in the control group.

Westphal *et al.*[26] conducted a 48-week, multi-center, randomized controlled trial of counseling and unsupervised exercise training vs. supervised physical training (24 weeks) followed by unsupervised training (additional 24 weeks). The supervised training was comprised of 45 minutes of stationary cycling and 30 minutes of resistance training twice a week. After 24 weeks, the supervised arm achieved a significantly higher maximum output in watt (132 ± 34, 95% CI: 117-147) compared to baseline 107 ± 25, 95% CI: 97-117, p = 0.012). In addition, output was higher in the supervised arm (115 ± 25, 95% CI: 105-125, p = 0.059) than in the unsupervised arm.

Hirschey *et al.*[27] conducted a randomized controlled trial of a home-based physical activity intervention (a booklet about physical activity for breast cancer survivors, that included narrative messages and writing and

thinking exercises) among 60 breast cancer survivors. Subjective exercise (weekly minutes) increased by two minutes, and objective exercise increased by 970 steps every four weeks in the intervention group compared to the control group ($p = 0.2676$ and $p = 0.0283$, respectively).

Bail *et al.*[28] conducted a 12-month randomized controlled trial of a home-based mentored vegetable gardening intervention among 82 breast cancer survivors. Compared with the controls, intervention participants reported significantly greater improvements in moderate physical activity and demonstrated improvements in the two-minute step test and arm curl ($p < 0.05$).

Lahart *et al.*[29] conducted a six-month randomized controlled trial of a home-based physical activity intervention involving 32 breast cancer survivors. Magnitude-based inference analyses revealed at least small beneficial effects on absolute and relative $\dot{V}O_2$ max (cardiorespiratory fitness), and total and moderate physical activity in the intervention compared to the usual care group.

4 Discussion

The results of this systematic literature review indicate that home-based exercise programs are effective in improving physical activity among breast cancer survivors who have completed primary therapy for the disease. A variety of outcomes were assessed in the trials, including self-reported minutes of physical activity, steps walked per day, functional capacity, cardiovascular endurance, body mass index, weight, sleep scores, quality-of-life, and attitudes toward physical activity. In the one trial that assessed bone mineral density as an outcome[6], no significant difference was observed between the two groups. A variety of intervention strategies have been tested in trials of home-based exercise programs, including aerobic and resistance exercise training, walking programs, print materials, telephone counseling, and gardening. A majority of the outcomes measured in the trials using one or more of the intervention strategies demonstrated positive change in the intervention groups compared to the controls. These studies yielded encouraging information and reflected the acceptance of innovative methods of physical activity interventions by breast cancer survivors.

Three studies of the effectiveness of home-based exercise programs focused on African American breast cancer survivors[11,19,25]. The results of these studies indicated that home-based exercise programs are effective in increasing physical activity and reducing weight among African American breast cancer survivors.

Four studies of the effectiveness of home-based exercise programs focused on women receiving aromatase inhibitor therapy for breast cancer[20,24,26]. The results of these studies indicated that home-based exercise programs are effective in reducing joint pain and increasing mobility among women receiving this therapy.

Two RCTs focused on using an email physical activity intervention among breast cancer survivors[17,18]. Both studies were effective using email, showing improvement with motivation readiness for exercise, diet, emotional functioning, depression and significant differences in physical activity.

Four studies on the effectiveness of home-based walking interventions focused on breast cancer survivors, with one of the groups in each study receiving hormonal therapy[13–15,21]. These studies demonstrated that home-based walking interventions are effective in increasing walking for exercise, reducing fatigue, and improving quality of life. Those receiving hormonal therapy reported improvement in sleep scores and increased serotonin levels.

With respect to limitations, outcomes, intervention strategies, and tests varied among the studies. Caution is therefore required in comparing results across studies. In addition, our literature review may not have captured all relevant studies.

In summary, home-based exercise programs are effective in improving physical activity among breast cancer survivors who have completed primary therapy for the disease. This includes women who are receiving aromatase inhibitor therapy for breast cancer. Home-based exercise programs, such as walking programs offer a convenient and affordable option for women who wish to increase their physical activity and maintain a healthy lifestyle.

Conflict of interest

The authors declare they have no conflicts of interest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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CASE REPORTS

Long-term survivors of advanced and metastatic lung cancer

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Abstract: The overall prognosis in patients with advanced and metastatic lung cancer is poor, however a subset of these patients has durable survival and they are called long-term survivors (LS). The definition of LS varies in published series from 18 months to 5 years. Few studies have focused on them. We report six cases of LS patients: three cases of non-small-cell lung cancer (stage IIIB and stage IV), two cases of small cell lung cancer, and a case of composite carcinoma (small cell carcinoma and squamous carcinoma), all having a survival of five years or more. Our patients show clinical and evolutionary similarities with LS in the literature regarding the prognostic factors associated with prolonged survival performance status and good response to first-line chemotherapy.

Keywords: lung-cancer, stage III and IV, prognosis, chemotherapy, survivors

Abbreviations

BMI: Body Mass Index
CD51: Cell Differentiation antigen 51
COPD: Chronic Obstructive Pulmonary Disease
CT: Computed tomography
CYFRA 21-1: Cytokeratin 19 Fragments 21-1
EGFR: Epidermal Growth Factor Receptor
Gm-CSF: Granulocyte-macrophage Colony Stimulating Factor
GOLD: Global Initiative for Chronic Obstructive Lung Disease
KRAS: K RAt Sarcoma oncogene
LC: Lung Cancer
LS: long-term Survivors
NSCLC: Non-Small Cell Lung Carcinoma
PS: Performance Status
SCLC: Small Cell Lung Carcinoma
TKI: Thyrosin Kinase Inhibitors

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1 Introduction

Lung cancers are frequent cancers with poor prognosis[1,2]. They are the leading cause of cancer-related mortality in men worldwide and represent therefore a major problem health[3]. However in clinical practice, very heterogeneous outcomes are observed between patients with locally advanced or metastatic non-small cell (NSCLC) and small cell carcinoma (SCLC)[4–6]. In fact, some patients will have prompt progression of the disease in spite of adequate treatments, on the contrary others will present a prolonged survival and will be called long-term survivors (LS). LS definition varies in published series, survival is greater than or equal to 18, 24, 30 months or 5 years[7–12]. Devoted studies are several. We report cases of 6 LS patients: 3 with NSCLC (IIIB and IV stages), one localized SCLC, one advanced SCLC and a case of composite carcinoma (SCLC and squamous cell carcinoma) who had all 5-year or more survival and we propose to review some literature data analyzing this topic.

2 Cases series

Table 1 shows the clinical features of all patients.

2.1 Case 1

A 52-year-old man, 90 packet-year smoker with a medical history of pulmonary tuberculosis 30 years ago, presented to us with isolated low abundance hemoptysis. Physical examination showed no abnormalities and performance status (PS) was normal (PS = 0). Chest

Table 1. Clinical features of all patients

Patient	Age/ Gender	Smoking status	Symptoms	TNM stage	Histological subtype	PS	First-line treatment	Outcomes	Second-line treatment	survival	Death
Case 1	52/Male	90 pack/year	Hemoptysis	IIIB T4N2M0	Adenocarcinoma	0	platinum and gemcitabine chemotherapy 3cycles	Almost complete regression	No	7 years	No
Case 2	46/Male	28 pack/year	Chronic cough & fever	IIIB T4N2M0	Squamous cell cancer	0	platinum and gemcitabine chemotherapy 3cycles+ radiotherapy	Almost total regression	No	6 years	No
Case 3	60/Male	no	Hemoptysis	Limited T4N2M0	small cell lung carcinoma (SCLC)	0	Platinium and etoposid chemotherapy 6 cycles + thoracic radiotherapy+ brain radiotherapy	Total regression	Yes : endoxan + adriamycin + etoposid	5 years	Yes
Case 4	45/Male	25 pack/year	Hemoptysis	Limited T4N2M0	SCLC+ Squamous cell cancer	0	Platinium and etoposid chemotherapy 6 cycles + thoracic radiotherapy	Total regression	No	6 years	No
Case 5	62/Male	100 pack/year	Dyspnea chronic cough	T4N2M1b	Squamous cell cancer	0	Concomitant platin-based-radio-chemotherapy+ Gemcitabine and Cicsplatin 3 cycles then Gemcitabine and carboplatin 3 cycles	Partiel regression then stability	Yes	8 years	No
Case 6	70/Male	80 pack/year	Hemoptysis	Extensive T4N2M1b	SCLC	0	Cisplatin and etoposid chemotherapy 6 cycles	Partiel regression then stability	No	5years	No

radiography showed right speculated hilar opacity. At bronchoscopy, an endobronchial mass obstructed completely the upper right lobe. Biopsy and cytology confirmed adenocarcinoma. Chest and abdomen Computed Tomography (CT) found a right upper lobe mass invading the mediastinum with lateral tracheal lymphadenopathy without distant metastasis. The tumor stage proved to be IIIB (T4N2M0). Three cycles of chemotherapy were conducted in previous delays associating platinum and gemcitabine at a dose of 75 mg/m^2 and 1250 mg/m^2. However the third cycle was complicated by a vagal attack with heart arrhythmia and low ejection fraction on transthoracic echocardiogram (45%). The checkup after 3 cycles showed an almost complete regression of the endobronchial mass in both bronchoscopy and chest CT. Considering complete response and heart toxicity, chemotherapy was discontinued. The patient is free of disease 8 years after chemotherapy.

2.2 Case 2

A 46-year-old man, active smoker (28 packs/year) who complained of 4-week history of cough and fever. His examination and PS were normal. Radiography showed a basal left speculated opacity. Fiberoptic bronchoscopy showed left lower lobe infiltration and an endobranchial mass obstructing the left basal pyramid.

Biopsy revealed well differentiated squamous cell carcinoma. Computed body tomography showed a tumor mass of the lower left lobe associated with subcarinal lymph nodes. We classified the tumor on stage IIIB (T4N2M0). He was treated by 6 cycles of chemotherapy based on platinium and gemcitabine followed by radiotherapy at the dose of 60 Gy. Endoscopic control noted complete regression of the basal pyramid endobranchial mass and imaging showed the persistence of basal peribronchial thickening. Therefore follow-up was decided. Seven years after, no recurrences of the disease have been noted.

2.3 Case 3

A 60-year-old man, nonsmoker, with a history of asthma was admitted in our department. He has been suffering from repetitive hemoptysis for about a month. His physical and general condition were normal (PS = 0)

Chest radiography noted a tumor mass of the right pulmonary hilum. Bronchoscopic examination revealed an almost complete occlusion of the right upper lobe with an endobronchial tumor whose biopsy had confirmed the diagnosis of small-cell cancer. Staging showed a mediastinal pulmonary mass measuring $50\times45\times45$ mm invading the right pulmonary artery associated with sub carinal lymph nodes and no distant metastases. So it's a limited SCLC. Thus the patient underwent 6 cycles of chemotherapy including etoposide and platinum every 3 weeks with concomitant mediastinal pulmonary radiotherapy at the dose of 60 Gy. Then a prophylactic brain radiotherapy was performed. Check-up tomography and bronchoscopy after radio-chemotherapy showed total regression of the tumor. Since then, the patient has had regular scans at the rhythm of 3 to 6 months. 3 years later, progression of the tumor has occured. Bronchoscopy noted reappearance of the upper right lobe mass and at tomography a trilobar massively necrotic mediastinal pulmonary complex with downstream lung collapse, associated to right lateral tracheal adenomegaly, right great abundance pleural effusion and costal and iliac lytic lesions. Considering preserved general state (PS = 0), the patient received 3 cycles of second line of chemotherapy including endoxan, adriamycin, etoposide and cisplatin. After the end of the chemotherapy the patient was lost for 7 months and then consulted again in a chart of profound deterioration of the general state (PS at 4), he died in few days in a table of respiratory failure . The overall survival for this patient was 5 years.

2.4 Case 4

A 49-year-old man, with a 25 packs/year smoking history, presented with a symptomatology of low abundance isolated hemoptysis since a month. Physical examination and general status were normal (PS = 0). The chest X-ray showed a suspected right-sided lateral tracheal opacity. At bronchoscopy there was an extrinsic compression aspect. The baseline thoracic-abdominal-pelvic and brain scan showed a $6\times4\times7$ cm upper right lobe mass with wide contact with the mediastinum, associated with right paratracheal adenopathy. Thoracoscopic biopsy of the mass confirmed the diagnosis of composite carcinoma with a contingent of squamous cell carcinoma associated with a SCLC. Considering limited disease, the patient received 6 cycles of chemotherapy combining etoposide and platinium at the classical doses in association with concomitant radiotherapy at the dose of 60 Gy. Post-treatment imaging showed almost complete regression of the tumor process with post-radiation sequelae lesions. Until now after 7 years, the patient experienced no recurrence of the disease.

2.5 Case 5

A 62-year-old man with a history of peptic ulcer disease and COPD GOLD3 was found to have marked right-sided mediastinal widening associated to right mediastinal and lung opacity compressing the trachea on routine chest radiograph for COPD exacerbation. He had no unusual symptoms apart from common exercise dyspnea and chronic bronchitis. On examination, he had inspiratory wheezing and digital clubbing. His PS was normal. Bronchoscopy revealed extrinsic compression of the lower third of the trachea and a bronchial tumor obstructing the lumen of the right main bronchus. Transbronchial biopsy and bronchial cytology concluded the diagnosis of poorly differentiated non-microcellular carcinoma. Baseline imaging staging showed laterotracheal confluent tumour and lymph node mass with an endoluminal tissue mass protruding into the right main bronchus with paratracheal and subcarinal lymphadenopathies. Skeletal Scintigraphy revealed acromial and sacroiliac metastases corresponding to stage IV (T4N2M1b). Thus the patient underwent firstly decompressive radiotherapy then 11 cycles of concomitant platin-based radio-chemotherapy. Post-treatment imaging showed partial tumor regression and repeated bronchoscopy had the same aspect. Bronchial cytology revealed the persistence of tumor cells. Therefore a second reading of the transbronchial biopsy had been performed to make sure weather a second line of chemotherapy is required. This later confirms the diagnosis of non-keratinizing poorly differentiated squamous carcinoma. Then the patient had received 3 cycles of chemotherapy including Gemcitabine and Cisplatin at the classical doses. The following CT revealed more partial tu-

mor regression and post-radiation sequelae so 3 other cycles of Gemcitabine in association with Carboplatin were added. After that the patient developed tumor progression in both CT and bronchoscopy corresponding to a time to progression of 19 months. He subsequently underwent taxotere second-line monochemotherapy during 6 cycles. Since that a semestral follow-up imaging was decided in association to supportive care. In fact the patient received several doses of bisphosphonates with significant improvement of bone pain. Currently no progression of the tumor and the metastases has been noted after an overall period of 8 years.

2.6 Case 6

A 70-year-old COPD GOLD 3 man, presented with a history of multiple episodes of hemoptysis of 6 months duration. Physical examination showed no appear abnormalities. His general condition was normal (PS = 0). Chest X-ray showed a suspected hilar opacity. Flexible bronchoscopy revealed infiltrated mucosa of the lower third of the trachea, the carina and all the right bronchial tree. Biopsy was nondiagnostic and branchial cytology confirmed the diagnosis of small-cell cancer. A subsequent computed chest, abdominal and brain tomography displayed a proximal right mediastinal and pulmonary tumor infiltrating the carina associated with ipsilateral paratracheal lymphadenopathy and multiple scattered hypodense liver lesions. Thus the tumor was classified as an extensive stage. Therefore the patient underwent 3 cycles of chemotherapy combining cisplatin and etoposide at the classical doses. First check-up CT scan showed tumor progression and appearance of left adrenal and bone metastases. However the liver lesions turned to be in fact biliary cysts. Hence it was decided to complete 3 other cycles of the same chemotherapy. The fifth cycle was complicated by severe anemia and neutropenia requiring transfusion of red blood cell and Gm-CSF respectively. The second follow-up CT and bronchoscopy noted overall stability. Then a quarterly physical and radiological follow-up was preconized. Since that the patient was lost to follow-up for 4 years. Meanwhile he consults for a moderate COPD exacerbation. The check-up tomography showed still the same findings. Despite duration of 4 years treatment-free, our patient experienced no tumor recurrence after accurately 5 years from the SCLC diagnosis.

3 Discussion

Lung cancer (LC) is a cancer with a poor prognosis[1]. The 5-year survival rates for all stages are 12% for men and 16% for women in France[2]. In Tunisia, recent epidemiological data are alarming: North-Tunisia cancer registries show an increase in the incidence rate from 22.4/100,000 in 1994 to 30.8/100,000 in 2003[3]. Among lung tumors, NSCLC account for over 80% of cases. 70% of them are diagnosed in an already advanced or metastatic stage. The median survival for stages IIIB and IV undergoing chemotherapy ranged from 7.9 to 11.3 months and the 2-year survival rates from 11 to 21%[4,5]. SCLC is a very aggressive cancer characterized by rapid loco regional and distant progression. Median survival is 14-16 months for patients with limited SCLC and 8-11 months for those with extensive form[6]. However, patients are often different and have heterogeneous response to the different treatments. Some of them will have favorable outcome and prolonged survival and will be called long-term survivors, these latter are defined by a survival most often greater than 2 years. The identification of the prognostic factors of LC survival has been assessed in several studies[12–16]. These prognostic factors are various and may be distributed as follows: Clinical criteria (age, smoking, comorbidities, quality of life, PS, *etc*.), The TNM classification (stage, lymph nodes staging..), Histological criteria (adenocarcinoma, SCLC, *etc*.), Biological criteria (platelet count, hemoglobin, leukocytes, lactate desydrogenase (LDH), *etc*.), and Genetic criteria (EGFR mutations, KRAS, *etc*.).

Among these trials, a recent study of late-stage NSCLC identified 5 prognostic factors associated with limited survival: fatigue, anorexia, desaturation, hyponatremia, and hypoalbuminemia with a high probability of death within 2 weeks if at least 3 of these factors are present (with a sensitivity of 100% and a specificity of 75%)[16]. Few studies investigating LS patients' features in advanced stages have been reported. Some of them interest patients included in clinical trials and therefore responding from the start to specific selection criteria, others are monocentric or have concerned different stages of NSCLC including early stages[12]. The main studies that have focused on NSCLC are summarized in Table 2. These studies have highlighted 2 major prognostic factors associated with long-term survival (in multivariate analysis): PS and first-line chemotherapy response. Baseline PS before chemotherapy is the most important prognostic factor predicting prolonged survival[12–22]. The characteristics of our patients joined these results: their PS were at 0 and they had responded well to a first-line treatment. The particularity of patients 1 and 2 is the fact the tumor mass has almost completely disappeared after a single course of chemotherapy. In Dujon study, the response to first-line treatment multiplied by 3 the probability of being a LS[12]. This result

Table 2. Summary of studies on long-term survivors (LS) of advanced and metastatic lung cancer

Autours	Collection data date	Cases number	Trial	Studied stages	2 year LS N (%)	Factors associated with prolonged survival in multivariate analysis
Finkelstein DM, 1986	1979-1983	893	Yes	IIIB-IV	36 (4)	PS 0 Alumina level
Sculier JP, 1994	1980-1991	1052	Yes	All stages (60,5% IV)	65 (6,2)	Chemotherapy response Early stage
Moro D, 1997	1982-1991	1551	No	All stages (59,9% III-IV)	15 (2)	PS Stage III
Satoh H, 1998	1985-1996	195	No	III et IV	14 (7,2)	N0 N1 Stage III
Julien S, 2000	-	120	No	All stages (47,5% IV)	20 (16,6)	Chemotherapy response
Okamoto T, 2005	1990-1999	222	Non	IV	17 (7,7)	N0-N1 Surgery
Satoh H, 2007	1998-2007	109	No	IIIB-IV	14 (12,8)	PS 0 Gefitinib
Dujon C, 2009	2002-2006	169	No	IIIB-IV	23 (13,6)	PS 0-1 TKI response
Wang T, 2010	1986-2001	846	No	III-IV	56 (6,6%) (5-year survival)	Resecable N2 T3N0 Single distant metastatic site
Giroux E, 2012	-	245	No	IIIB-IV	39 (15,9%)	Surgery Maintenance chemotherapy PS 0-1 Tumor progression >3 months LDH level Number of chemothrapy lines
Van Damme V, 2013	March-August 2009	NP	No	IV	31	Chemotherapy response Number of chemothrapy lines
Chen YZ, 2014	1999-2013	206	No	IV	28(13,6%)	PS Chemotherapy response Chinese medicine treatment

was also reported by Sculier: the response to chemotherapy multiplied survival by 2.2[13]. Recently, in the Van Damme prospective study, 34 LS patients were compared to 31 patients with a survival of less than 2 years, the response to chemotherapy was a predictor of long-term survival (p = 0.001)[22].

Thyrosin kinase inhibitors (TKI) are recent molecules in the treatment of advanced LC. This class was therefore not analyzed in older retrospective series in the literature. None of our patients received TKI due to its unavailability in our country. In Dujon trials, receiving a TKI appears as an independent survival factor, with a survival probability greater than 2 years multiplied by 1.9[12].

This report has also be observed in a recent Japanese study of 109 patients with advanced LC in which using gefitinib treatment was a survival prognostic factor in a multivariate analysis[14].

Prognostic SCLC factors are also various and are comparable to those in NSCLC. A recent Japanese study conducted on SCLC patients receiving third-line chemotherapy showed that prognostic factors before the start of third-line chemotherapy are: low level of LDH, high BMI (body mass index), normal hemoglobin level, a good response to second-line chemotherapy and progression delay after second-line chemotherapy[17]. Limited data are available about LS in SCLC. That's may be explained by: the prompt progression delay as well as acquisition of second-line or third-line resistance to chemotherapy, whose efficiency is debatable[18,19].

A Korean multicenter study published in 2014 retrospectively analyzed 295 patients with SCLC. Among them, 51 (17.3%) patients had a survival higher than 2 years with a mean of 42 months. Predictive factors of long-term survival were: PS 0-1, extent of the disease, and CYFRA 21-1 level[15]. Considering these factors, a prognostic index was elaborated to define four groups of patients with an average survival for each estimated to 22.7, 13.7, 8.5, and 3.2 months. In our study, SCLC patients' features were consistent with literature data. In fact they had a good PS at 0 and an early stage of the disease at presentation. In our patient with SCLC (patient 3) progression occurred 3 years after first-line treatment. This very long delay without any treatment is not frequently observed in SCLC. One case of SCLC with a 7-year survival after diagnosis was reported, this patient had received radiotherapy associated with several lines of chemotherapy and somatostatin analogues treatment[6].

The coexistence of SCLC and NSCLC has been reported in scarce cases[20,21]. Factors implicated in the development of this entity have not been well studied because of its rarity. Some authors have suggested its association with heavy smoking leading to p53 and KRAS gene mutations[21].

In a recent genetic study of 7 cases of patients with a composite tumor, 6 of them expressed CD51 and synaptophysin in the 2 tumor quotas. The authors concluded that there is a common tumor cell clone at the origin of these tumors that may explain the existence of genetic similarities[22].

Very limited data are available to evaluate composite tumors prognosis. We didn't find in literature trials analyzing this issue. For our patients with a composite carcinoma, the long survival could be explained by the limited quota of SCLC, its PS at 0 and the good response to first-line chemotherapy.

Comparing characteristics of our NSCLC to LS in literature, patients 1 and 2 had clinical and evolutionary similarities. In fact these latter were particular by complete response after only 3 cycles of first-line chemotherapy and with a 6-year follow-up without recurrence, the disease could be declared cured. For patient 5 who had a stage IV squamous cell cancer survival until now exceeds nearly 8 years. As for patient 3 with limited SCLC he is particular by long stability delay without progression during 3 years with any treatment.

4 Conclusion

All these data confirm that NSCLC advanced stages and SCLC LS exist and that thanks to the advent of novel therapies their number as well as survival duration are increasing.

In the next future, better identification of long-term survival factors based on clinical and genetic studies could better select this group and further improve survival.

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CASE REPORT

Hepatocellular carcinoma associated to Behçet's disease

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Abstract: The occurrence of hepatocellular carcinoma (HCC) on a healthy liver is exceptional and represents a real diagnosis challenge for the clinician. Recently a particularly increased risk of cancer during Behçet's disease (BD) was reported by several studies. Only a few sporadic cases of liver cancer associated with this vascultis have been reported. We report an original observation of non-fibrolamellar HCC occurring on healthy liver in a Tunisian patient followed for BD. A 43-year-old man, followed since the age of 25 for BD with isolated cutaneous and mucosal involvement, and treated by colchicine, was admitted for exploration of a pain of the right hypochondrium evolving since a few months associated with an important slimming, anorexia, and evening fever. The clinical examination noted a firm and painful hepatomegaly. Radiological exploration (ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI)) showed a bulky hepatic tumor with highly developed arterial blood supply. Ultrasound-guided biopsy concluded at HCC without signs of fibrolamellar type or cirrhosis. Biological tests were without abnormalities and specific investigations eliminated underlying chronic hepatopathy (chronic viral hepatitis B or C, hemochromatosis, Wilson's disease or autoimmune hepatitis). The patient was treated symptomatically given the advanced stage of cancer. He quickly died after a month because of a multi-organ failure. HCC on healthy liver is exceptional and BD was suggested as a possible contributing factor. Thus, regular radiological monitoring seems to be recommended in any patient followed for BD, especially those with hepatic veins thrombosis.

Keywords: liver cancer, Behçet's disease, hepatocellular carcinoma, vasculitis, non-cirrhotic liver

1 Introduction

Hepatocellular carcinoma (HCC) occurs in more than 80% of cases in pre-existing liver injury (cirrhosis or other chronic non-cirrhotic liver disease)[1,2]. Rare cases can develop on previously healthy liver; specifically fibrolamellar carcinoma[3]. Apart from this particular histological type, chronic hepatitis C (CHC) on healthy liver remains exceptional[4,5].

Behçet's disease (BD) is a non-specific systemic vasculitis that is particularly common in young people around the Mediterranean and the old Silk Road[6]. Recently a particularly increased risk of cancer during this disease was reported by several studies[6–8]: standardized incidence ratio (SIR) at 2.13-3.10[9] and Hazard Ratio (HR) at 1.134[10].

Only a few sporadic cases of liver cancer associated with BD have been reported[9–13], and in large series like the South Korean series of 14,137 patients with BD, the frequency of HCC did not exceed 0.20%[10].

We report an original observation of non-fibrolamellar HCC occurring on healthy liver in a Tunisian patient followed for BD.

2 Observation

43-year-old man, followed since the age of 25 for BD with isolated cutaneous and mucosal involvement (recurrent oral ulcers, genital ulcers, pseudo-necrotic folliculitis, positive Pathery-test, and positive HLA B51), and treated by colchicine, was admitted for exploration of a pain of the right hypochondrium evolving since a few months associated with an important slimming, anorexia, and evening fever.

The clinical examination noted a firm and painful hepatomegaly. Abdominal ultrasound showed a round, heterogeneous tumor, measuring about 10 cm long axis, and developed at the expense of left lobe of the liver (Figure 1). Abdominal CT confirmed these findings and objectified the significant arterial blood supply of this tumor (Figure 2 and Figure 3). This tumor compresses the right portal vein without signs of thrombosis or loco-

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regional extension. There was no intra-abdominal lymphadenopathy, ascites, direct or indirect signs of cirrhosis or portal hypertension.

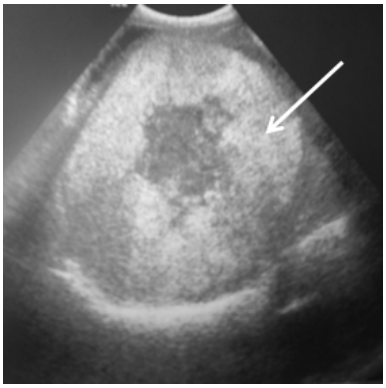

Figure 1. Abdominal ultrasound: Bulky heterogeneous tumor of the left lobe of the liver

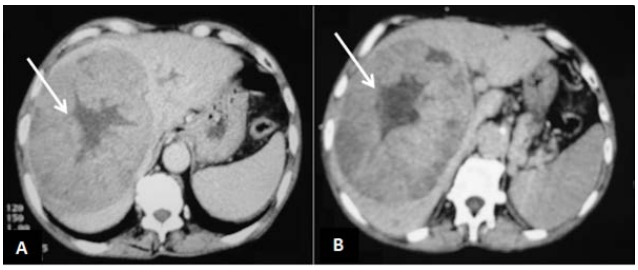

Figure 2. Axial abdominal CT without contrast injection (hepatic dome (A) and hepatic hilum (B) sections): large and heterogeneous liver tumor with central scar

Nuclear Magnetic Resonance Imaging (MRI) revealed a well-limited, encapsulated mass of heterogeneous signal with a central hyposignal scar on T1, hypersignal on T2, and unmodified signal after gadolinium injection. The peripheral region of the mass has a T1 intermediate signal, T2 heterogeneous hyposignal, and a heterogeneous contrast enhancement (Figure 4 and Figure 5).

The echo-guided biopsy puncture concluded with HCC. No characteristic signs of fibrolamellar carcinoma were noted.

The biological assessment, in particular transaminases, prothrombin rate, factor V of the hemostasis, gamma-glutamyl transferases, lactecodehydrogenases, electrophoresis and immunoelectrophoresis of serum proteins, and the alpha fto-protein, was without abnormalities. The serologies of viral hepatitis B and C were also negative. Serum iron, cupremia, cupruria, serum ceruloplasmin, and immunological status (antinuclear antibodies, anti-Liver kidney microsome type 1 antibodies, anti-mitochondrial M2 antibodies, and anti-smooth muscle antibodies) were within normal limits, thus eliminating underlying chronic hepatopathy (chronic viral

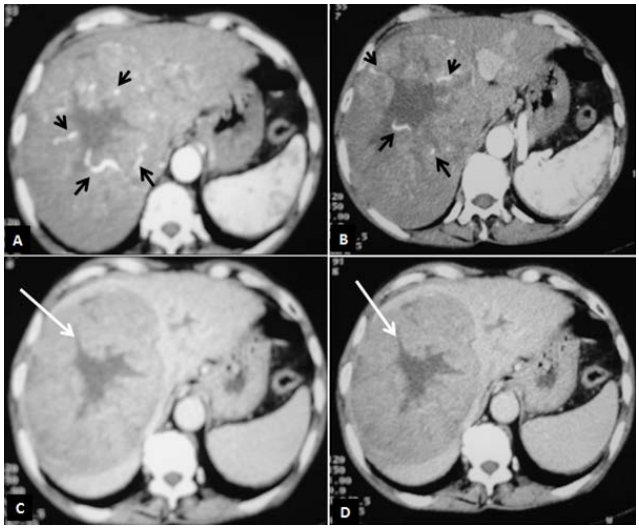

Figure 3. Axial abdominal CT with contrast injection (different vascular times: early arterial (A), late arterial (B), hepatic (C), and delayed phase (D)): heterogeneous aspect of the liver tumor (white arrow) with significant arterial blood supply (black arrows)

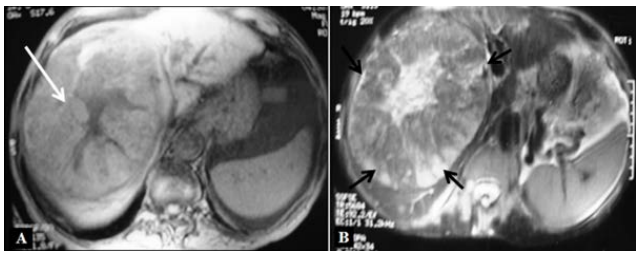

Figure 4. T1-weighted without contrast (A) and T2-weighted (B) axial hepatic MRI: heterogeneous aspect of hepatic mass (white arrow) with extensive arterial vascularization (black arrows)

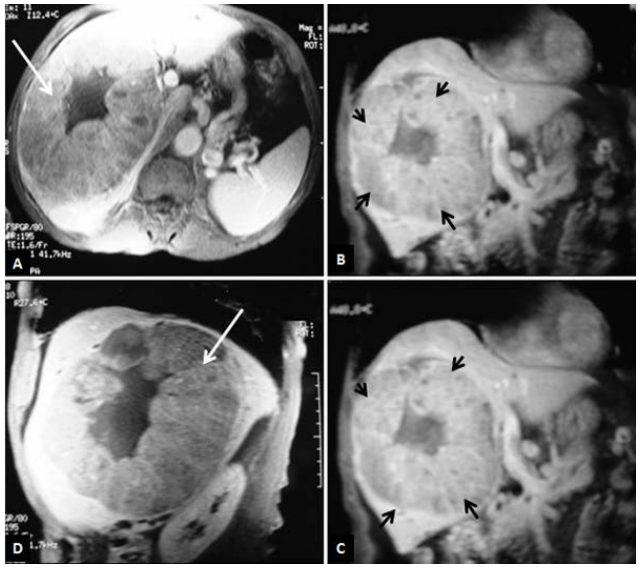

Figure 5. 3D T1-weighted hepatic MRI with contrast injection (different vascular times: early arterial (A), late arterial (B), late portal (C), and delayed phase (D)): heterogeneous aspect of the hepatic tumor (white arrow) with extensive arterial blood supply (black arrows)

hepatitis B or C, hemochromatosis, Wilson's disease or autoimmune hepatitis).

The patient was treated symptomatically given the advanced stage of cancer. He quickly died after a month because of a multi-organ failure.

3 Discussion

The development of HCC on previously healthy liver is exceptional[5]. This eventuality represented only 0.32% in the largest series of Giannini EG *et al.* of 3,027 cases of HCC[14].

Diagnosis is based, according to global recommendations, on the combination of medical imaging and histology[2,15,16]. The radiological aspects are very suggestive of the diagnosis. Ultrasound and CT presentations are the same as those of HCC on cirrhotic liver; size greater than 2 cm and intense arterial vascularization are very suggestive of the diagnosis[2,17].

MRI is considered superior to all other medical imaging techniques: ultrasonography, CT and positron emission tomography (PET-scan) for the diagnosis of focal liver injury[1,16,18]. The MRI aspect, especially on the T1, T2, diffusion, and sequences with gadolenate dimeglumine (Gadobenate dimeglumine-BenzylOxy-Propion -ic Tetraacetic Acid (Gd-BOPTA)) or gadoxetic acid (Gadolinium-EthOxyBenzyl-Diethylene Triamine Pentaacetic Acid (Gd-EOB-DTPA)) is the most specific of HCC on healthy liver[1,16,18].

HCC incidence increases with age, and the maximum of cases is diagnosed around the age of 70[1]. The young age of our patient would be another argument in favor of the promoting role of BD in the genesis of this liver cancer.

Indeed, the risk of any cancer during BD was significantly higher in the multiple nationalwide population-based studies compared to the general population: standardized incidence ratio (SIR) was 3.10 in men and 2.13 in women with BD in Jung YS *et al.* series[9], SIR was 1.5 in all patients and 1.8 in female patients with BD in Wang LH *et al.* study[19], and Hazard Ratio (HR) was 1.134 in Na SJ *et al.* series[10].

However, liver cancer remains exceptional in BD: 2 patients out of 512 with BD in the Turkish series of Bayraktar Y *et al.* (0.39%)[20] and 22 patients among 14,137 in the Korean series of Na SJ *et al.* (0.20%)[10]. The majority of cases were hepatocellular carcinoma[9–12], more rarely other types of liver cancer were reported: malignant hepatoma[12] and liver leiomyosarcoma[13].

The risk of elevated hepatic carcinogenesis associated with BD was confirmed by the Korean national study of Jung YS *et al.*, where SIR to develop hepatic cancer during this disease was equal to 4.00 compared to the general population[9].

The exact mechanism promoting carcinogenesis associated with BD is still unclear. It appears to be multifactorial involving persistent chronic inflammation, immune dysfunction, vasculitis, and some immunosuppressive therapies used in this disease[6,8–10,20].

For HCC, thrombosis of the hepatic veins may also be a possible contributory factor[20]. BD is known to be a condition with very high thrombogenic risk, and hepatic veins are often affected during this vasculitis[21].

No data were found in the literature regarding the clinical peculiarity of HCC in BD (incidence of ascites, portal vein hypertension, *etc.*); These data are difficult to specify because BD is also associated with a high risk of thromboembolism explaining the frequency of thrombosis of portal veins and portal hypertension even outside HCC[21]. Similarly, ascites can be part of the particular digestive involvement of this disease (entero-Behçet), regardless of the existence or not of an associated HCC[6,8–10,20].

Similarly, no specific recommendations have been found in the world literature concerning the periodicity of the clinical and radiological monitoring of these patients.

4 Conclusion

HCC on healthy liver is exceptional and BD was suggested as a possible contributing factor. Regular radiological monitoring (hepatic ultrasonography) thus seems to be recommended in any patient followed for BD in order to diagnose early hepatic degeneration. Subjects with BD with thromboembolic complications, particularly thrombosis of the hepatic veins, appear to have a significantly higher risk of developing liver cancer.

Conflicts of interest

The authors declare that they have no conflict interest.

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CASE REPORT

Optimal management and the role of radiotherapy in the complex treatment of primary mediastinal seminoma: A clinical case with literature review

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Abstract: The Primary Mediastinal Seminoma (PMS) is a rare extragonadal malignant germ-cell tumor. We report a clinical case of our practice, which is the reason for this literature review and try to find the optimal multimodal therapeutic option and the role of radiotherapy.

Keywords: seminoma, mediastinum, complex treatment, radiotherapy

1 Introduction

Seminoma is a rarely diagnosed extragonadal germ-cell tumor, which occurs in three ectopic places: the pineal gland[1], retroperitoneal space[2] and mediastinum[3].

The mediastinum is the most frequent place for this localization (25%-30%). Due to the rarely diagnosed cases, insufficiently studied origin and more specific biological behaviour, mediastinal seminoma poses a number of unresolved therapeutic problems. Therapeutic problems are related to the multimodal treatment approach and the location of each of the oncological methods: surgery, radiotherapy and chemotherapy.

2 Case presentation

A 32-year old male was diagnosed with vena cava syndrome and enlarged supraclavicular lymph node. Not reported for concomitant oncological diseases. Thorax CT showed a big tumour mass occupying the anterior portion of the mediastinum, infiltrating 2/3 of the right lung and compressing the trachea, vena cava and vena azygos, clearly indicated in Figure 1.

The biopsy of the supraclavicular lymph nodes permitted the diagnosis of seminoma.

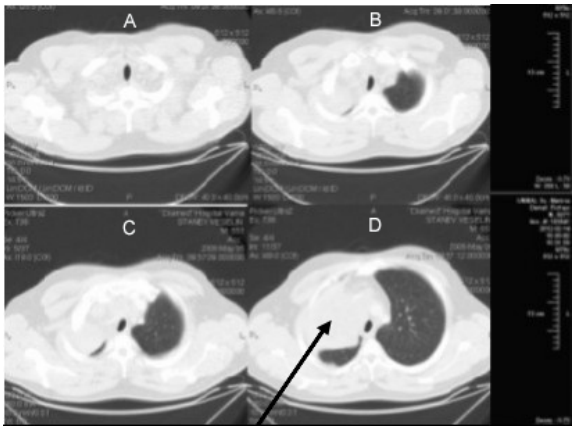

Figure 1. Thorax CT before chemotherapy and radiotherapy (A→B→C→D stand for the different levels from top to the bottom of the chest)

Blood laboratory tests for β-subunit human chorionic gonadotropin (b-hCG) and Alpha Fetoprotein (AFP) before chemotherapy were in normal ranges (b-hCG, 5 IU/l; AFP, 4.03 IU/ml). Bone scan with gama-camera (Tc 99 m and abdominal ultrasonography) were also normal. The treatment started with chemotherapy with PVB-Carboplatin (200 mg/m^2) on day 1, Vinblastine (0.15 mg/m^2) on days 1 and 2, Bleomycin (15 U/m^2) on days 1 and 2 (every 21 days, 6 cycles were done). Due to partial response (PR) that decrease in the initial tumour volume to 50%, chemotherapy was followed by radiotherapy (Figure 2).

At the first stage of radiotherapy the whole mediastinum was irradiated of telegamatherapy with single dose (2 Gy) to a total dose (TD, 42 Gy). For the supraclavicular region and neck lymph nodes were implemented TD (40 Gy) with a single dose (2 Gy). Control CT of the

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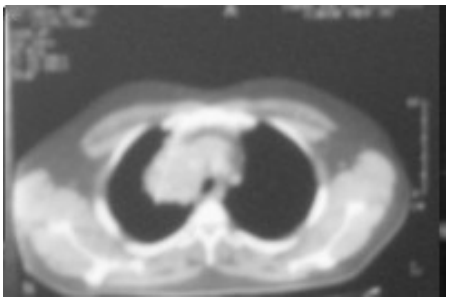

Figure 2. Control CT of the chest after 6 cycles of chemotherapy (similar to Stage II)

chest was performed after the first stage and the image revealed residual tumour mass in the mediastinum (Figure 3).

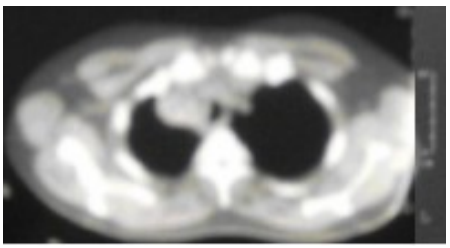

Figure 3. Control CT of the chest after 6 cycles of chemotherapy and radiotherapy of the mediastinum to total dose 42 Gy (similar to Stage II)

At the second stage of radiotherapy was implemented boost to the TD (56 Gy) in the residual tumour mediastinal mass. New control chest CT will be performed two months after the radiotherapy. If the tumour persists, maybe surgery will be a good option?

3 Discussion

For determination of the optimal treatment management in PMS, it is necessary to consider all characteristics of this rare extragonadal germ-cell tumor.

Malignant Mediastinal Germ-cell Tumors (MMGT) are 3%-10% of all mediastinal tumors and only 1%-5% of Germ-cells tumors. Primary Mediastinal Seminoma is 52% of all MMGT. This cancer can occur at any age, but is most common between the ages of 20 and 40. The patient complains of dyspnea, retrosternal pain or heaviness in this area, cough, fever, gynecomasty and weight loss. In 10% of the patients superior vena cava syndrome develops[4,5].

PMS is a slowly increasing tumor that reaches up to 20-30 cm in diameter[6]. Most often this is a bulky disease with large, heterogenic tumor masses in the anterior mediastinum and very rarely in the middle mediastinum[7].

These tumours can infiltrate the neighboring tissues and organs: lung, heart, chest wall. They can lead to obstruction of pulmonary arteries and to infiltration of the pericardium[8]. The dissemination is usually present with symptoms from lymphatic infiltration (supraclavicular and neck lymph nodes on both sides).

In 30%-40% of the cases the disease is localized without distant metastases. It is possible to have hematogenic dissemination, most often in the bone[9], lung and intrathoracal structures and rarely in the retroperitoneum and in the brain[10].

Laboratory blood tests and biochemistry are in normal ranges. Serum levels of b-hCG and AFP are in normal ranges too. In the 10% of the locally advanced PMS /pure seminoma/ there may be elevation of b-hCG levels, but not AFT. A significant elevation of AFT levels (up to 100 ng/ml) usually indicates the presence of the nonseminomatous germ-cell elements. AFP levels may be elevated in patients with liver dysfunction or hepatitis.

Germ-cell neoplasms are classified into two broad histologic categories: seminoma and non-seminomatos germ-cell tumours. Pure seminoma is the most common single histology, accounting for 30% of all germ-cell tumours[7]. Germ-cell tumors are composed of round, large pleomorphic cells with clear or granular cytoplasm with large centrally situated nucleoli.

The principal objective of the staging evaluation is to ascertain whether the patient has an early-stage disease or disseminated disease.

A chest-X-ray can determine a tumor mass in the mediastinum without calcifications and compression into trachea and bronchi. Chest CT in most cases reveals tumor mass in the anterior mediastinum, situated around the trachea, superior vena cava, vena azygos with infiltration of these structures. CT imaging is non specific and that's why it is difficult to differentiate PMS from other mediastinal tumors. Using MRI, it is possible to differentiate seminoma and nonseminoma germ-cell tumors.

For exact staging the following are necessary: testicular ultrasonography, abdominal ultrasonography, chest CT, abdominopelvic CT and PET-CT with Gallium-67[11].

Treatment options are surgery, radiotherapy, chemotherapy and complex therapy. In literature there are cases of local surgery, excision of the primary mediastinal tumour, including with thymectomy[7]. With regard to thymectomy, it is not indicated, since the previous notions are rejected, that the tumor originates from the thymus or from its embryonic chins. Radical inguinal orchiectomy is a rejected method too, because the old statement that PMS are metastases from degenerative occult primary testicular tumours is not acceptable now. In pathology reports after autopsy no changes are found in the testis or in the retroperitoneal lymph nodes[12,13].

The modern opinion on the role of surgery in PMS is as "salvage surgery": (1) In case of residual mediastinal tumour masses after chemotherapy[14,15,31]; (2) Relapses despite the achieved local tumour control after chemotherapy[16]. Resection of the residual tumour masses with a diameter of less than 3 cm after chemotherapy should be fine-tuned, as the athohistologists often report lack of tumour cells. The residual tumor masses after chemotherapy must be over 3 cm in order to require a "salvage surgery"[17].

Seminomas are radiosensitive tumors. Radiotherapy alone in PMS achieves a disease-free progression period (FDP) up to 54%-62% and overall survival of up to 69%[18,19]. The standard radiotherapy plan, Clinical Target Volume (CTV), includes mediastinum, supraclavicular and neck lymph nodes with TD (40-50 Gy)[29]. In neck lymph nodes metastases, some oncologists expand the volume of radiotherapy, including axillary lymph nodes. Total dose with cancer eradicating effect in PMS when the radiotherapy is applied alone is 45 to 60 Gy. 1/3 Of the patients after radiotherapy have distant metastases or local relapse[20]. The most frequent reason for relapse is the bulky disease and the systemic characteristics of this illness. Chances to cure PMS patients only with radiotherapy and to confirm local tumour control (LTC) are slim.

Since 1970, the standard medical treatment in PMS is 4 to 6 cycles of chemotherapy with Cisplatin[16,21,22] or PVB. Tumor evaluation after chemotherapy in most cases reports remission of the disease. High dose chemotherapy followed by bone marrow transplantation is given in dissemination diseases[24–27]. Chemotherapy alone achieves high therapeutically results that 5 years of FDP is 86%-90%[19,28]. Liu TZ, *et al*. recommended that chemotherapy combined with a local therapy such as surgery or radiotherapy is a reasonable treatment strategy[32]. In the presented clinical case, it concerns locally advanced mediastinal seminoma with vena cava syndrome and partial tumour response after chemotherapy, similar to other authors[29]. In the residual tumour mass, we realized TD 56 Gy. This radiotherapy is necessary, because surgery was impossible and it is the only follow-up treatment in the present case. There is no significant shrink in the tumour volume after chemotherapy and also after radiotherapy to TD 42 Gy which is a sign of moderate chemo- and radioresistance. Despite normal levels of β-HCG, in the tumour there may be present a small amount of syncytiotrophblastic cell component, which does not increase the tumour marker. This is the reason for the second stage to raise the mediastinal TD to 56 Gy.

PMS is a bulky disease with systemic characteristics. For maximal treatment effect it is necessary to combine three oncological methods: chemotherapy, radiotherapy and salvage surgery[30]. In all cases one should start with chemotherapy, and after that proceed with radiotherapy like an additive method. Because of radio sensitivity and accumulation of side effects of radio and chemotherapy, the TD must be up to 54-56 Gy. The patient follow-up is every 2 months including chest CT and serum markers.

4 Conclusion

(1) PMS is a systemic disease with a high chance to be cured.

(2) The role of radiotherapy is additive local treatment method following chemotherapy.

(3) An open question remains whether the salvage surgery should be performed with a residual tumor after chemo and radiotherapy.

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Thanks Letter to Peer Reviewers

All members of Current Cancer Reports (CCR) editorial office would like to extend greetings and sincere thanks to the peer reviewers. Thanks for their invaluable professional service to CCR. Without their help, it would not be possible for the journal to finish this full year of existence with 5 high-quality articles published by 24 different authors.

For next issue, CCR will continue to make efforts to improve the quality and service level of manuscript submission. We look forward to their continuous cooperation with us to improve the quality of manuscripts and contribute to the development of CCR.

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