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LETTERS TO THE EDITOR

Do concurrent targeted treatments and radiotherapy cause additional acute side effects

Dear Editor,

As with many cancers, the clinical course of breast cancer varies in parallel with treatment. Nowadays, improvements have been maintained, including prolonged complete response, and overall, disease-free and progression-free survival. However, with new treatment strategies, especially after targeted therapies, new complications have been seen besides previously reported acute/chronic toxicities [1-3].

One of the targeted therapies in breast cancer is trastuzumab. It was developed against human epidermal growth factor receptor 2 (HER-2). It is effective in both early and late stage of breast cancer when combined with other drugs. Trastuzumab exerts antitumor activity through both disruption of HER-2/neu receptor and arrest of the cell cycle in the G1 phase. In addition, it suppresses angiogenesis by reducing the expression of endothelial growth factor [1,2].

Overall survival advantage was shown after trastuzumab treatment in metastatic breast cancer patients and use of this drug as adjuvant has been on the agenda recently [1-3]. In the analysis of North Central Cancer Treatment Group NCCTG N9831, National Surgical Adjuvant Breast and Bowel Project NSABP B-31, Herceptin Adjuvant Trial HERA, The Breast Cancer International Research Group BCIRG 006 and FinHer study, trastuzumab use as adjuvant was shown to reduce recurrence up to 50% and to increase survival rate [1-5]. It has been co-administered with radiotherapy and chemotherapy drug combinations in sequential treatment strategies but, this kind of partnership can bring additional side effects which are not known exactly yet. Currently, trastuzumab is being used in advanced disease and usually in combination with other chemotherapy drugs, hormonal therapy and radiotherapy. With combination, the goal here is the creation of clinical synergism.

Trastuzumab is used in combination with other anticancer drugs and it can be administered alone without serious side effects even in the long-term use. Unlike chemotherapy, trastuzumab has its own specific toxicity. Cardiotoxicity which is seen clinically as congestive heart failure is the most frequent complication. Albeit small, there is also pulmonary toxicity risk [1-5].

During radiotherapy for breast cancer, lung, esophagus and heart are the organs at risk that come to mind first. In parallel with radiation dose and effected volume within the radiotherapy region, various side effects are seen at early/late stages. Radiotherapy-induced side effects are: at early stages, pneumonia in the lung, dermatitis on the skin, pericarditis in the hearth, and at late stages lung and skin fibrosis, coronary artery disease and cardiomyopathy [1,2]. During treatment, in order to minimize these side effects, a careful planning of radiation dose and target organ volume is necessary. Factors that could lead to consequences such as concurrent chemotherapy drugs, comorbidities and patient status are other important factors adding in toxicity.

The mean follow-up time is less than 5 years in studies about the targeted breast cancer treatment with concurrent or sequential radiotherapy. Belkacemi et al. compared simultaneous trastuzumab and radiotherapy with 3-week trastuzumab and they observed increased acute toxicity in skin, lung and heart with trastuzumab-RT [3]. Bellon et al. reported grade 2 and 3 skin toxicity in 48% and 5% respectively for weekly and 3-week co-administered trastuzumab and radiotherapy [4]. In the Perez et al. study, simultaneous implementation of weekly trastuzumab+RT was found to decrease acute skin toxicity [1]. Halyard and his colleagues compared the application of trastuzumab+RT RT versus RT alone to patients in the North Central Cancer Treatment Group phase III trials. When both groups were evaluated according to acute skin toxicity, there wasn't any difference for skin, interstitial pneumonia, dyspnea and esophagitis, but increased risk of toxicity was reported for heart [2]. In the work of Raben et al., concurrent trastuzumab versus external beam radiation therapy alone were compared for grade 2 and above acute toxicity. For Karnofski performance status, weakness, edema, skin reaction and mastalgia no significant differences were shown between the groups [5].

In conclusion, toxicity is seen mostly in skin, lungs, heart and esophagus with the use of trastuzumab with RT, concurrently or sequentially. Because the use of this agent together with radiation therapy reduces normal tissue tolerance, frequency and severity of toxicity that may occur are not known exactly. During radiotherapy, toxicity will be assessed better with careful planning of the treatment area size and normal tissue size in the application area. Especially, addition of trastuzumab to radiotherapy or increase in the volume of normal tissue in the treatment region, acute and chronic effects are expected to increase. Analyses and assessments on this matter will shed light in the evaluation of adverse effects.

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Should addition of five years of ovarian suppression to tamoxifen be "must" for hormone receptor positive and HER-2 positive breast cancer under the age of 35?

Dear Editor,

Hormone receptor-positive and HER2- positive breast cancer patients younger than 35 years may be at higher risk of recurrrence. Standard chemotherapy and trastuzumab are standard therapies for early-stage breast cancer. NCCN guidelines commonly recommend 5 years of aromatase inhibitors with ovarian suppression, especially for younger patients. NCCN guidelines also commonly recommend tamoxifen and ovarian suppression [1]. However, duration of ovarian suppression was not described. International expert consensus favored a period of 5 years of ovarian suppression, especially in patients at higher risk of relapse such as younger age and/or with HER2-positive disease [2]. Furthermore, the SOFT study also showed a benefit of 5 years of tamoxifen plus ovarian suppression over tamoxifen alone, especially in younger breast cancer patients. Exploratory analysis for HER2-postive population was not performed due to the rarity of HER2-positive breast cancer patients [3]. Alltogether, addition of 5 years of ovarian suppression to tamoxifen should be "must" for hormone receptor-positive and HER-2 positive breast cancer patients under the age of 35.

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Does trainee involvement in Ivor Lewis esophagectomy impact outcomes in any way: A question looking for an answer

Dear Editor,

We read with great interest the original article recently published in the *Annals of Surgery* journal entitled "Trainee Involvement in Ivor Lewis Esophagectomy Does Not Negatively Impact Outcomes" [1]. The authors demonstrated, through a prospectively maintained database of 323 esophagectomized patients, that trainee involvement in esophageal cancer operations is not associated with adverse patient outcomes. In particular, patients were divided into 4 cohorts according to whether a consultant or trainee performed the abdominal and chest phase; group 1: Consultant both phases; group 2: Consultant abdomen and registrar chest; group 3: registrar abdomen and consultant chest and group 4: registrar both phases [1]. No difference was found between patients operated by consultants and patients operated (totally or partially) by trainees in terms of blood loss, lymph node yield, length of hospital stay, perioperative morbidity and mortality as well as 2-year survival [1]. However, are these results of high evidence?

First, the authors did not specifically record in their results the Body Mass Index (BMI) distribution among the four groups of patients, leaving room for a possible occult systematic bias, i.e. the assignment of patients with higher BMI - and consequently more challenging cases - to be operated on by consultants. This may also account

for the difference in the ASA status between the four groups, where a tendency was shown for consultants to more frequently perform the chest phase of patients with ASA grade of 3 or above (i.e. patients with morbid obesity (BMI ≥40 or severe systemic disease) [1,2].

It is well known that obesity, besides technically challenging for surgeons, is often associated with a higher rate of postoperative complications, including respiratory complications and anastomotic leaks in patients operated for esophageal cancer [3]. Although not consistent in the literature, obesity may also compromise overall and disease-free survival, both in patients with esophageal adenocarcinoma [4] or squamous cell carcinoma [5]. Therefore, trainees may have been involved in procedures considered to be technically more straightforward rather than those deemed of high risk.

Second, another systematic bias that may have been overlooked is the determination of the "operating surgeon". According to the authors, the "operating surgeon" title was attributed at the end of the operation to a trainee or consultant, depending on the percentage of the operation performed by each [1]. However, it is not clear whether the "operating surgeon" was in all cases the one starting the operation. How valid is the authors' definition of the "operating surgeon" in a case started initially by a trainee that was taken over intraoperatively by a consultant due to arising difficulties? Also, who is the "operating surgeon" in a case where 75% of the procedure is performed by a trainee but the rest 25%, which is performed by the consultant, includes the most demanding surgical steps? Indeed, possible changes of roles between the trainees and the consultants during the surgical procedure, which are not recorded in the "operating surgeon" data, may have caused a selection bias in favor of trainees operating the more straightforward cases.

Interestingly, though, the aforementioned methodological issues cannot be overcome due to obvious ethical reasons. No randomized controlled trials can be conducted to answer the question about the impact of trainee involvement in esophagectomies, so that a higher level of evidence can be achieved. All in all, trainee involvement and surgical training are imperative; however, patient safety should always remain the cornerstone of our surgical practice.

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Reducing dietary argininine restriction may decrease the metastatic potential of primary breast cancer

Dear Editor,

Asparagine is known worldwide as the first amino acid that was isolated from its natural source. Asparagine is also known for its key role in the biosynthesis of glycoproteins. In addition, it is also essential for the synthesis of many other proteins. Human nervous system also needs this amino acid to be able to maintain an equilibrium. Asparagine increases the resistance to fatigue and improves the smooth functioning of the liver. It is also necessary for transformation of amino acid from one form to another.

The most common typical dietary sources of this amino acid include beef, chicken, dairy products, seafood and eggs. As for vegetarians, they may find helpful to consume asparagus, soy and whole grains to get more amino acid from them [1].

Most breast cancer patients did suffer from metastatic disease instead of primary tumor during the follow-up. For cancer cells to become metastatic, they must leave the primary site, enter the vascular circulation, survive in the blood, and then extravasate and colonize secondary sites. Asparagine synthetase expression in a breast cancer patient's primary tumour was most strongly correlated with later metastatic relapse [2]. Interestingly, a recent study using mice as a model of breast cancer showed that limiting asparagine by knockdown of asparagine synthetase, treatment with l-asparaginase, or dietary asparagine restriction reduces metastasis without affecting the growth of the primary tumour, whereas increased dietary asparagine or enforced asparagine synthetase expression promotes metastatic progression [3]. These results suggest that simply reducing dietary argininine restriction may decrease the

metastatic potential of primary breast cancer in humans. This issue needs to be determined by clinical studies in breast cancer patients.

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Irreversible electroporation for Stage III locally advanced pancreatic cancer: Single-center experience

Dear Editor,

Pancreatic adenocarcinoma (PC) remains a devastating disease with a 5-year survival rate not exceeding 6%. It is a highly lethal malignancy due to the obstacles that have been imposed concerning its early detection. 50% of patients with advanced pancreatic cancer have metastatic disease and an additional 25-35% present at that stage with borderline resectable PC or with locally advanced unresectable PC.

New ablation techniques for locally advanced PC (LAPC) that remain unresectable even after neoadjuvant chemo(radio)therapy due to their spread to vital structures, such as irreversible electroporation (IRE), use electrodes which deliver high-voltage electricity directly to the tumor under radiological control have been developed. Therefore, apoptosis is induced due to nanopores that are created irreversibly in the cell membrane. It is very important to notice that it influences only the cells inside the non-thermal ablation area of the tumor [1]. It has been proven that IRE is safe for vascular and ductal structures and, in addition, it does not harm the supporting connective tissue. This fact makes this method suitable for the treatment of LAPC.

In this retrospective single-center study we report on 10 patients with radiographic and biopsy-proven stage III pancreatic head or body cancer that received open IRE with intraoperative ultrasound imaging, using the Nanoknife IRE device. After treatment with IRE, an early imaging was performed to identify early postoperative complications. Chemotherapy started early post operatively in consensus with the oncologists and all patients were evaluated with computerized tomography every month. Tumor volume was measured and recorded using computed tomography (CT). Complications were recorded at 90 days and were classified with the Clavien - Dindo classification system.

Ten patients, with a median age of 62 years underwent IRE for locally advanced pancreatic head cancer (n=7) and body cancer (n= 3). All patients were treated successfully with an open IRE approach. Five patients experienced grade II (Clavien-Dindo) procedure-related complications. There were no grade 3 to 5 complications. Median follow up was 10 months. Tumor volume decrease at 6-month imaging follow up was found in 80% of the patients (n=8). Local disease progression was observed in one patient, while no evidence of metastatic disease was noticed in any patient. One patient died at 6 months after IRE. Median overall survival time was not reached, but mean survival time was estimated to be 16.7 months (95% CI, 14.2-19.1). Outcome data for all patients can be seen in Table 1.

In this study we report a 50% complication rate, but most were grade 2 complications and there was no mortal-

Table 1. Outcome data per patient

Patient no.	*Sex*	*Age (years)*	*Tumor location*	*Pre-IRE treatment*	*Tumor volume decrease (%) at 6-month follow-up*	*Survival after diagnosis (months)*	*Surival after IRE (months)*	*Current status*
1	M	57	Head	GemOx	64.7	20	18	Alive
2	M	61	Head	GemOx	36.6	17	14	Alive
3	F	64	Head	Gemcitabine	60.5	17	14	Alive
4	M	62	Head	GemOx	36.9	16	12	Alive
5	F	48	Head	GemOx	62.6	12	10	Alive
6	F	54	Body	-	54.9	10	8	Alive
7	M	62	Head	GemOx	49.7	14	10	Alive
8	M	66	Body	GemOx	20.1	10	6	Alive
9	F	73	Body	Gemcitabine	32.6	7	6	Dead
10	M	70	Head	GemOx	0	6	4	Alive

Data derived from 3-month follow-up imaging

ity in our patients. Morbidity rates ranged from 26 to 37% in Martin et al. [2] and Kluger et al. [3] reports, two of the biggest reports on IRE in LAPC. IRE has also been tested in increasing surgical resection margins in borderline PC as shown by Marsanic et al [4].

IRE is bringing new hopes in the treatment and management of LAPC. The majority of studies on the efficacy and safety of this method are based on nonrandomized series, but have shown that IRE is encouraging in terms of overall patient survival [5]. Nonetheless, it is an expensive technique with risks of complications. Hence, it needs to be ratified in large randomized prospective studies.

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Which nut fights stage III colon cancer better?

Dear Editor,

There are many types of nuts including walnuts, almonds, Brazil nuts, cashews, hazelnuts, macadamias, peanuts, pecans, pine nuts, pistachios. Nut consumption is known to reduce the risk of obesity, diabetes mellitus, and cardiovascular disease [1]. Furthermore, dietary fiber is supplied by almonds and walnuts and oleic acid is provided by hazelnuts; both of these components are known to be cancer-protective [2,3]. Fadelu et al. [4] carried out a prospective, observational study of 826 eligible patients with stage III colon cancer who reported dietary intake on food frequency questionnaires while enrolled onto a randomized adjuvant chemotherapy trial. They concluded that diets with a higher consumption of nuts may be associated with a significantly reduced incidence of cancer recurrence and death in patients with stage III colon cancer after a median follow-up of 6.5 years. However, what remains uncertain is that which nut is potentially more effective in decreasing colon cancer recurrence and death. Lastly, it is important to know the potential mechanisms that nuts can inhibit colon cancer cells.

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Is exercise a 'must' for breast cancer survivors: Yes, it is!

Dear Editor,

Exercise is associated with significant reductions in the recurrence and mortality rates of several common cancers including breast cancer. Breast cancer survivors who do effective excersise can potentially benefit from reduced levels of fatigue, and improved quality of life, physical function and body composition (i.e. ideal body mass index). The amount of activity required to achieve effective prevention is moderate (e.g. walking 30 minutes per day at 2.5 miles per hour) [1]. The American College of Sports Medicine dictates that exercise is generally safe for most breast cancer survivors, and inactivity should be avoided [2]. Exercise during and following treatment has been as-

sociated with reductions in breast cancer recurrence and disease-specific mortality rates of 30% to 60% [3]. However, many oncologists do not take into account the importance of the appropriate exercise recommendations in breast cancer survivors. Survivors with lymphedema, peripheral neuropathy and breast reconstruction should follow specific precautions. In conlusion, providing the oncologists with the training and tools needed to provide adequate exercise recommendations to breat cancer survivors is 'must' to improve patient outcomes.

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