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Choosing wisely in oncology: necessity and obstacles

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ABSTRACT

In the last decades, the survival of many patients with cancer improved thanks to modern diagnostic methods and progresses in therapy. Still for several tumours, especially when diagnosed at an advanced stage, the benefits of treatment in terms of increased survival or quality of life are at best modest when not marginal, and should be weighed against the potential discomfort caused by medical procedures. As in other specialties, in oncology as well the dialogue between doctor and patient should be encouraged about the potential overuse of diagnostic procedures or treatments. Several oncological societies produced recommendations similar to those proposed by other medical disciplines adhering to the Choosing Wisely (CW) campaign. In this review, we describe what was reported in the medical literature concerning adequacy of screening, diagnostic, treatment and follow-up procedures and the potential impact on them of the CW. We only marginally touch on the more complex topic of treatment appropriateness, for which several evaluation methods have been developed (including the European Society for Medical Oncology—magnitude of clinical benefit scale). Finally, we review the possible obstacles for the development of CW in the oncological setting and focus on the strategies which could allow CW to evolve in the cancer field, so as to enhance the therapeutic relationship between medical professionals and patients and promote more appropriate management.

PATIENTS AND PHYSICIANS IN THE TURMOIL OF PROGRESS

Cancer will remain a medical emergency in the next decades. By 2030, a 70% increase of cases is expected due to the global population growth and ageing. Two-thirds of cancer deaths will happen in low-income to medium-income countries.[1 2]

Although fortunately some tumours can be cured, many others remain highly problematic despite technological progresses (higher knowledge of disease biology, substantial progress in surgery, medical and radiation oncology) and multidisciplinary approach to diseases. With continual technological expansion and the enthusiasm that it can raise, the potential risk of medical choices is to overestimate efficacy and clinical benefits, or respectively to underestimate the discomfort caused to the advanced disease patient for whom the advantage of diagnostic and therapeutic interventions is at best modest. Based on a more rigorous application of evidence-based medicine (EBM), a higher attention is today given to a cautious use of diagnostic and therapeutic resources, to maintain the interest of the patient at the centre.[3] This balance can be obtained through an important interaction between the clinician (knowing better about diagnosis, prognosis, therapeutic options and chances of success in each particular set) and the patient (personal experience of the disease, social and family influences, role of the media, attitude to taking risks, personal expectations and preferences).

CHOOSING WISELY IN ONCOLOGY: THE COURAGE TO ADVANCE

Choosing Wisely (CW) was initiated in 2012 by the American Board of Internal Medicine (ABIM). By defining the patients' needs as a priority, its goal was to favour, thanks to shared and informed choices, the dialogue between physicians, other health professionals and patients on the topics of diagnostic tests, treatments and procedures, which were at risk of being inappropriate.[4] Thanks to the support of the Commonwealth Fund, of medical societies and associations, CW is now active in >20 countries. In the oncology community, CW has now been actively supported only by the main North American societies, which have published own recommendations on exams, procedures and treatments considered inappropriate, and which are summarised in table 1. In 2013, the American Society for Clinical Oncology (ASCO) published a list of 10 procedures concerning on one hand general treatment aspects and on the other hand topics on screening, staging and surveillance, particularly for breast cancer (BC) and prostate cancer.[5] In the same year, the American Society of Hematology (ASH) published a list of five procedures, which are at risk of being overused.[6] Some of these recommendations were supported by solid evidence (ie, against the liberal transfusion of erythrocytes concentrates), others were chosen because lacking convincing evidence

Table 1 Choosing wisely in oncology: recommendations by societies

Society procedure	ASCO	ASH	ASTRO	SSO
Therapy	*Overall, cancer-directed* No therapy for solid tumour when: PS 3–4, no benefit from prior interventions, no eligibility for clinical trials, no strong evidence supporting the clinical value of further anticancer treatment. No combination chemotherapy when treating metastatic breast cancer, unless a rapid response to relieve tumour-related symptoms is needed. No targeted therapy unless tumour cells have a specific biomarker that predicts an effective response to the these agents. *Supportive care* No WBC-stimulating factors for primary prevention of febrile neutropaenia in patients with <20% risk for this complication. Antiemetics should be adapted to the likelihood of severe or persistent chemotherapy-induced nausea and vomiting.	*Overall* No routine use of inferior vena cava filters in patients with VTE. No plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (ie, outside of the setting of major bleeding, intracranial haemorrhage or anticipated emergent surgery). *Supportive care* If transfusion of RBCs is necessary, transfuse the minimum number of units to relieve symptoms or to return to a safe HB range (7–8 g/dL in stable, non-cardiac inpatients).	*Overall* No routine use of RXT hyperfractionated schedules (>10 fractions) for palliation of bone metastases. No RXT in non-curative setting without defining the goals of treatment and considering palliative care referral. No routine adjuvant whole brain RXT to stereotactic radiosurgery for limited brain metastases. *Breast* Consider shorter RXT schedules after conservative surgery in women aged ≥50 years with early stage invasive cancer. No routine use of IMRT to deliver whole RXT after conservative surgery. *Prostate* Consider active surveillance in low-risk prostate cancer. No routine use of proton beam therapy. *Endometrial* No RXT following hysterectomy in low-risk disease. *NSCLC* No routine RXT in R0, N0-1 resected disease.	
Staging	*Prostate* No PET, CT and bone scans in the staging of early prostate cancer. *Breast* No PET, CT and bone scans in the staging of early breast cancer.			*Colorectal cancer* No routine PET-CT as staging for localised disease or as part of surveillance after surgery. *Breast cancer* No routine sentinel node biopsy in clinically node negative women aged ≥70 years with hormone receptor positive invasive cancer. *Melanoma* No routine imaging in patients localised with primary cutaneous melanoma, unless suspicion for metastatic disease.
Surveillance	*Breast* No surveillance biomarkers or imaging (PET, CT and bone scans) for asymptomatic curatively treated patients. No routine PET or PET-CT surveillance for cancer recurrence detection in asymptomatic patients who complete initial treatment, unless there is high level of evidence that such imaging will change the outcome.	*Lymphoma* Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma.	*Breast* No mammograms more often than annually after RXT following sparing surgery.	*Colorectal cancer* No routine blood tests other than carcinoembryonic antigen.
Screening	*Prostate* No PSA testing in asymptomatic men when they are expected to live <10 years.	*Thrombophilia* No test in patients with VTE occurring in the context of major transient risk factors (surgery, trauma or prolonged immobility).		*Breast cancer* No routine breast MRI in average risk women

ASCO, American Society for Clinical Oncology; ASH, American Society of Hamatology; ASTRO, American Society for Radiation Oncology; IMRT, intensity modulated radiotherapy; NSCLC, non-small cell lung cancer; PSA, prostate-specific antigen; PS, performance status; RBC, red blood cells; RXT, radiotherapy; SSO, Society of Surgical Oncology; VTE, venous thromboembolism; WBC, white blood cells.

of benefit while inducing potential harms and costs (as the use of caval filters or CT scan surveillance in aggressive lymphomas). The American Association for Radiation Oncology (ASTRO) identified 10 therapeutic procedures, particularly concerning gynaecological, prostate and lung neoplasia, which were published in 2014 in the setting of the top five recommendations.[7] Finally, in 2016 the Society of Surgical Oncology (SSO) also gave its indications on procedures considered to be inappropriate; this was limited to the domains of screening, staging and surveillance of colorectal cancer (CRC), BC and melanoma.[8] To our knowledge, there are currently no other published recommendations in English language on CW arising from other national societies in the cancer field.

DID THESE FIRST STEPS HAVE ANY CONSEQUENCES?

At 5 years from the launching of the CW campaign, a first evaluation of its impact in general medical disciplines can be drawn. According to an inquiry of the ABIM for the years 2014 and 2017, there have not been major changes neither in terms of doctors sensitisation to CW (21% in 2014, 25% in 2017), nor in terms of doctors difficulty (42% in 2014, 46% in 2017) to discuss with their patients the appropriateness or not of some procedures.[9] Besides, in a study considering seven procedures at risk of inappropriateness, significant changes have been observed only in two of them.[10]

And what about the impact of CW in oncology? We report here the published data analysing the appropriateness of some screening, diagnostic and follow-up procedures, classified by pathology and by type of interventions considered. We will further touch on the methods which have been developed to evaluate the appropriateness of cancer treatment, and the impact of the CW on the application of these evaluations to clinical practice.

Lymphoma

Surveillance

The ASH recommended against systematic use of CT scan in aggressive lymphoma surveillance. A study of patients with diffuse large B-cell lymphoma showed that still an important proportion of these patients was undergoing surveillance CT scans (cumulative incidence 52.5% during a 3-year follow-up), although with a tendency to reduction in 2014 compared with 2006 (48% vs 62.4%, p<0.001).[11]

Breast cancer

Staging

The SSO stated that women with BC above 70 years of age with endocrine responsive tumour and negative lymph nodes should not undergo routine sentinel lymph node excision. The recommendation was based on a study on 190 000 patients aged 70–90 years with the above-mentioned characteristics in whom lymph node involvement was detected in only 15% of cases.[12] These patients had a higher chance to receive chemotherapy (28.3% vs 5.5%, p<0.001), endocrine treatment (83.6% vs 71.4%, p<0.001), radiotherapy to the preserved breast (81.4% vs 73.6%, p<0.001) and postmastectomy radiotherapy (30.3% vs 5.1%, p<0.001). Another study in 71 000 women aged >70 years with BC, negative lymph nodes and endocrine responsive tumour, confirmed that some clinicopathological factors (grade 1, cT1mi-T1c, or grade 2, cT1mi-T1b) represented low-risk criteria for positive lymph nodes compared with those who did not fulfil the same criteria (7.8% vs 22.3%; response rate 2.86, p<0.001); therefore, in the presence of this low-risk criteria the sentinel lymph nodes analysis could be omitted.[13] A retrospective study examining the use of radiology in the period between 2008 and 2015 in 34 000 patients with a newly diagnosed BC stage 0–II, showed that the use of PET, CT and bone scan was significantly reduced over time in stages 0–IIA (p<0.001), while it remained stable in stage IIB.[14] Another study in 1100 women with early stage disease showed that 21.8% of patients underwent radiological staging, of which 28% underwent CT, 21% PET, 34% bone scan and 6% MRI.[15] These exams were more frequently requested in the presence of triple negative disease, young women (aged <50 years) and more advanced stages (stage IIb vs stage ≤IIa, p<0.001).

Surveillance

A retrospective study in women undergoing lumpectomy and accelerated partial breast irradiation showed that a short interval mammographic surveillance (median interval between the end of radiotherapy and the four first mammographic follow-up exams where 6, 6, 9 and 12 months, respectively) could not detect relapses earlier. The authors concluded that mammographic surveillance should be performed annually, with the first tests done at 12 months.[16] Despite the lack of evidence, radiological imaging with newer and more sophisticated methods and biomarkers dosing are frequently used in the surveillance of women with early stage disease. In a study of 6600 patients, 24% of patients underwent at least one radiological exam and 28% at least one tumour marker analysis.[17]

Prostate cancer

Screening

Serum prostate-specific antigen (PSA) should not be measured in asymptomatic patients above 70 years of age.[18] Still, in a large Canadian cohort PSA screening was performed in 55.5% of patients aged >70 years, more frequently in subjects with high social economic conditions and easier access to specialists.[19]

Staging

After issuing CW recommendations in 2013, the Canadian Urological Association evaluated the use of bone scan at diagnosis of low risk prostate cancer. Among 27 174 patients identified from 2008 to 2017, the ordered bone scans decreased not significantly from approximately 24% to 20%.[20]

Colorectal cancer

Screening

It is well established that screening programmes produce a drop in both incidence and mortality from CRC in both genders.[21] All CRC screening strategies (faecal occult blood test (FBOT), faecal immunochemistry, stool DNA tests, sigmoidoscopy, colonoscopy and virtual colonoscopy) are cost-effective compared with no screening, but studies are conflicting as to which method should be preferred.[22]

In a systematic review on the utilisation of colonoscopy and sigmoidoscopy in the general average-risk population in different countries (23 studies from the USA and 20 studies from other countries), estimates from the USA were highest, continued to increase over the past decade and reached 62% for colonoscopy use within 10 years in people aged 50–75 years in 2012. Conversely, endoscopy use in other countries was substantially lower (12%–44% for lifetime colonoscopy use and 13%–30% for recent colonoscopy use), except for Germany, where 55% of the screening-eligible population reported colonoscopy utilisation within the previous 10 years in 2008–2011. Both lifetime and recent endoscopy use increased with age and peaked at approximately 70–75 years.[23]

In a retrospective study in subjects whose initial colonoscopy showed advanced adenoma, non-advanced adenoma or no adenoma, adherence to surveillance guidelines was variable with reports of overutilisation in low-risk groups (subjects without adenomatous polyps) and underutilisation in high-risk groups (subjects with a history of advanced adenoma).[24] Following EBM guidelines can help reduce the cost and risk of unnecessary procedures, and prevent cancer in high-risk individuals. Through CW, the American Gastroenterological Association recommends against repeating CRC screening (by any method) for 10 years after a negative colonoscopy result, and screening no earlier than 5 years after removal of a low-risk adenoma in asymptomatic patients.[25]

In a study of patients undergoing dialysis, approximately 12% of them underwent a screening test (sigmoidoscopy or FBOT), particularly the subjects considered to be at low risk of death and in a proportion so high to raise the suspicion that a possible overuse of this screening procedure was applied in this population.[26]

Surveillance

The majority of patients with CRC undergo post-treatment surveillance, the rationale for which is that early detection of recurrent disease amenable to other curative therapies can improve survival. Other reasons include detection for potential use of palliative therapies (even prior to symptom onset) and improvement in quality of life (QoL). Most surveillance guidelines include a combination of visits with history and physical examination, imaging, colonoscopy and measurement of the carcinoembryonic antigen.[27 28] There is modest variation in the guidelines of other national societies, such as those of the ASCO, the American Society of Colon and Rectal Surgeons and European Society for Medical Oncology (ESMO), which recommend a shorter duration of surveillance overall (annually thoracic and abdominal CT scan for 3 years in most cases).[29–31] Of note, European societies tend to subscribe to a much less intense surveillance programme than those commonly used.[32]

Nevertheless, controversy continues to surround the optimal surveillance protocols. In patients with stage I–III CRC, a systematic review and meta-analysis was conducted to find evidence for the effectiveness of monitoring in advancing the diagnosis of recurrence and its effect on survival. By examining 16 randomised trials, more intensive surveillance anticipated the diagnosis of recurrence by a median of 10 months; no demonstrable difference in OS was observed in 10 of 11 studies reporting survival outcomes. In addition, by analysing seven randomised clinical trials published from 1995 to 2016 in which 3325 patients were randomly assigned to more intensive versus less invasive follow-up protocols, no OS difference emerged between the two groups.[33] The benefit of surveillance after curative treatment of stage IV CRC is even more controversial, but might be justified because repeat resection can improve OS and 20% of these patients are eligible for such treatment with potentially curative intent. No trials have assessed the optimal follow-up approach after curative resection of CRC metastases, and similarly to surveillance of patients with stage I–III disease, most programmes are more intensive during the first 3 years than at later time points.

Lung cancer

Staging

The Society of Thoracic Surgeons recommends to avoid radiological examination of the brain in patients with non-small cell lung cancer (NSCLC) in early stage and without symptoms. Still, in approximately 650 patients with clinical stage IA, 12% underwent at least one neuroradiological exam, without detecting any metastasis.[34] Additionally, another study on approximately 3800 patients with NSCLC, stage IIB, IIIA or IIIB, reported overuse of bone and PET scan compared with the guidelines in 25% of patients.[35] However, it must be underlined that not all guidelines are consistent among themselves and with the CW recommendations: in lung cancer to continue on the same example, the ESMO guidelines recommend PET scan as a mandatory diagnostic procedure for accurate lymph node mediastinal staging and radiation planning, although the level of evidence is corresponding to IIIA.[36]

Surveillance

In a study of 66 000 patients of the SEER database, aged <66 years and undergoing curative resection for stage I–IIIA NSCLC or stage I–III CRC, the use of postoperative follow-up PET scan at 6 and 18 months was evaluated in the time frame between 2001 and 2009. While in 2001, 11% of patients with NSCLC and 4% of patients with CRC underwent a PET scan, in 2009 these proportions significantly increased (25% and 13%, respectively, p<0.001).[37]

In a recent randomised trial, two follow-up programmes of surveillance were studied in patients with curatively resected stage I–IIIA/T4 N0-2 NSCLC. After a median follow-up of almost 9 years, no significant OS difference (8.2 vs 10.3 years; HR 0.92, p=0.27) was observed in the standard arm (chest X-ray) compared with the experimental arm (thoracoabdominal CT scan plus bronchoscopy).[38]

Cervical cancer

Screening

In a Norwegian study in women not vaccinated against human papillomavirus (HPV), a mathematical model could define that the frequency and the age of starting HPV screening had a major impact in the reduction of cervical cancer incidence (from 90.9% to 96.3%) compared with no screening at all. On the other hand, an intensified surveillance of HPV-positive women with negative cytology did not add any significant advantage in terms of risk reduction.[39]

Supportive treatments

In a study of almost 680 000 patients treated with chemotherapy, an overuse of antiemetics compared with the ASCO CW recommendations was reported in 24.8%, mainly in patients receiving endovenous chemotherapy. After 6 months from the CW recommendation by ASCO, only transient reduction of 7% of antiemetics use was observed.[40]

Miscellaneous

A systematic review of 59 articles evaluated the overuse of imaging procedures or therapies: the majority of considered studies were conducted in the USA, and referred to adults and elderly people. Underlying how problematic it can be to extend the intervention area of CW, this study focused on imaging exams in low-risk BC and prostate cancer, and only a few of the analysed studies were centred on active oncologic treatment.[41] Chest X-ray is often recommended in haematology patients with neutropenic fever. In a retrospective analysis of 435 patients admitted with neutropenic fever, chest X-ray rarely detected pulmonary infection (2.4%) or changed management (1.1%) in the absence of respiratory symptoms or signs.[42]

Two studies examined the concordance with CW recommendations among oncologists in the USA. In the first report examining the so-called top five ASCO recommendations, the highest concordance (range 78.4%–83.3%) was seen on the recommendation not to prescribe chemotherapy in patients with reduced performance status, the lowest concordance (range 67.7%–74.2%) was related to the use of biomarkers or imaging in the surveillance of women with early stage BC.[43] In the second analysis on almost 38 000 patients, important variations (between 39% and 94%) were seen on the concordance concerning ASCO and ASTRO recommendations, with significant variability among 12 cancer centres adhering to the study.[44]

Referring to the Canadian indicators of CW, a study estimated that 740 000 screening exams for BC and cervical cancer were performed outside of the recommended age, and that within 1 year of diagnosis approximately 17 000 patients underwent inappropriate treatment.[45] In a Swedish cohort of >500 000 elderly patients, it was observed that patient dying of cancer were more prone to receive poly-medication during the last year of life.[46] In this cohort, drugs were prescribed which were indicated for non-life-threatening comorbidities and which were potentially dangerous because of their pharmacological interactions; other studies suggested similar findings.[47 48] ASTRO recommends not to use hyperfractionated radiotherapy in patients with symptomatic bone metastasis. To verify the compliance with this suggestion, a study performed in the USA reported that the adoption of standardised patient pathway had as a consequence a reduction in the use of hyperfractionated schedules, lowered from 18.6% in the years 2003 to 2008, to 15.2% in the years 2009 to 2013 and to 9.7% in 2014.[49]

To summarise, evidence underlying the need for CW in oncology was mainly generated by retrospective cohort studies. Some studies suggest the futility of some procedures, while other studies report the evolution of these procedures over time, underlying the potential for change. The main study topics are the ones on staging and surveillance procedures, while prospective studies oriented to pharmacological treatment are almost lacking.

OBSTACLES TO THE DEVELOPMENT OF CW IN ONCOLOGY

As in other sectors of medicine, in oncology also there are barriers in the process of change towards a clinical practice where it is understood that doing more does not necessarily mean treating better.

Clinicians' perceptions and beliefs

Medical practice sometimes implies futility, and this is true for oncology as well. Nevertheless the attitude of doctors towards CW is not enthusiastic, as the data described above seem to imply. Although it could be believed that the CW initiative would easily obtain the consent of the oncological medical community, the evidence suggests that the gap between the CW vision and the clinician is still quite wide.

In our institute, we addressed the CW topic twice during meetings of the senior medical and nursing staff. Some of the considerations expressed on these occasions were:

- '…we are already working according to the principles of CW…'
- '…some of the recommendations are trivial and useless…'
- '…some recommendations are not applicable to our reality…'.

In the same line, a national oncology academic, when asked about CW in oncology said that "I think everybody agrees on the CW initiative. Thus, speaking for myself the issue is not really intellectually stimulating".

These considerations probably reflect the thought of a large sector of the medical community, leaving little space to self-criticism and opportunity for change. If we recognise that building an awareness to CW is a complex path, the best chances of success depend on obtaining a deep personal involvement in addition to an involvement of the institutions and of the society.

The doctor-patient relationship: a balance of expectations, requirements and influences

A frequently evoked argument against making rational and EBM choices in oncology practice is the clinician's difficulty towards a patient's or family member's requests to perform medical procedures, although not recommended or based on solid scientific evidence. Is the problem of the over-requiring patient really frequent? In a study in which doctors and nurses were interviewed, only 8.7% of patients requested diagnostic or therapeutic procedures, and these were considered inappropriate only in 1% of cases.[50] In the specific case of advanced disease, this can be addressed by explaining clearly the prognosis and the realistic benefits that can be expected from the requested procedure, illustrating the alternatives while knowing that, with appropriate modulation, the majority of patients desire detailed prognostic information.[51–53] If this transparency is omitted, the patient could be induced to require futile care, with potential negative consequences on his QoL.[54] Because we live in an era of progress in cancer treatment, we should be careful not to induce inadequate expectations. This concept of 'therapeutic illusion' was evoked for the first time in 1978 and recently rediscovered.[55 56] It is also important that doctors keep away from the general belief that 'it is better to do something rather than do nothing' or from the idea that active treatment is a good mean to preserve hope or reduce the emotional burden of patients.[57] Learning to communicate is therefore a basic aspect. Physicians should be taught early about communication, from the university and all along the career. Health professionals should be offered the necessary instruments so that they would not feel uneasy when discussing prognosis or end of life and should be given instruments to help patients during the coping process. Doctors must keep being instructed in order to maintain a clinical sense, which is nowadays sometimes sacrificed in favour of technology. Finally, doctors should also be reminded of the necessity to offer patients other information sources (ie, cancer societies and leagues) in order to guarantee a real plurality of information on appropriate medical procedures.

CW and scientific evidence: how can they get along?

As described, the evidence that 'doing less is better' is limited, and this could be an alibi for looking at CW with suspicion. CW should therefore become a clinical research area in oncology, with similar dignity as other more traditional research domains, usually more prestigious and gratifying. Still, even though science and regulatory authorities put us in the condition to 'be allowed to do', is the evidence always robust enough concerning the cost-benefit relationship of interventions? This calls for some considerations.

The concept of clinical care value is becoming more popular; the value of therapeutic strategies is calculated as a ratio of the clinical benefit size towards the economic costs and towards stress and distress for the patient. ESMO and ASCO have both developed instruments allowing doctors (and patients as well) to weight the value of single oncological treatments.[58–60] The two tools present similarities and some conceptual differences. The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) for solid cancers is meant to influence policy decision makers, while ASCO value framework has been developed for all cancers to facilitate the dialogue between physicians and patients in assessing the value of new cancer therapies. ESMO-MCBS is applied to comparative studies, while ASCO value framework allows single-arm trials evaluation by using response rate. Both tools are subdivided into two subframeworks to reflect curative and palliative settings, computing clinical benefit, toxicities and QoL. QoL is only part of ASCO value framework for palliative care, while it is considered in the curative setting in ESMO-MCBS. For the palliative setting framework, ESMO-MCBS clinical benefit is modulated according to OS or PFS in the control arm, which is not the case in ASCO framework. ESMO-MCBS allows the evaluation of immature data with high disease-free survival for potentially curative treatments, while ASCO framework awards bonus point depending on the survival curve tail for both settings. ASCO framework additionally includes bonus points for palliation of symptoms and/or treatment-free interval for palliative care. Finally, ASCO framework considers therapy cost (but not as part of scoring), which is not taken into account in ESMO-MCBS. By using these instruments, out of 277 phase III studies (40% BC, 31% NSCLC, 22% CRC, 6% pancreatic cancer), only 21% reached the level of significant clinical benefit.[61] Similarly, using the ESMO criteria, only 37 out of 51 anticancer drugs approved in metastatic disease by the Food and Drug Administration (FDA) between 2000 and 2015 reached the threshold of clinical benefit, namely levels 4 and 5 of the scale.[62] Similar low scores of clinical benefit emerged for the systemic treatment of advanced neuroendocrine gastro-entero-pancreatic tumours.[63] For the majority of 48 anticancer drugs approved by the European Medicines Agency between 2000 and 2013, the survival benefit was quite modest (from 1 to 5.8 months, median 2.7 months) and only in 10% of them an improvement in QoL was demonstrated.[64] For targeted therapy in kidney cancer, only 36.4% of studies obtained a high clinical benefit score, and only when adding the QoL criteria to progression-free survival.[65] A high clinical benefit level compared with costs was reported in eight phase III studies of patients with NSCLC treated with anti-EGFR TKI.[66]

Producing robust efficacy data allowing the translation of new experimental technologies (in particular new

drugs) to the real-world population is a difficult task, and regulatory agencies play a key role in controlling the speed of the approval process.[67–70] Methodologic aspects can influence the development of drugs: when, as it increasingly happens, surrogate end points are accepted as criteria for drug approval by the FDA, the survival advantage will be either unknown or absent for many drugs.[71] Publication bias, which can concern the authors, the journals, the reviewers and also the readers can as well influence therapeutic choices. As to the latter, a summary interpretation of the results of clinical trials can induce the clinician to overestimate the real benefit of a therapeutic intervention.[72]

Defensive medicine

Clinicians sometimes order exams, procedures or treatments for fear of being accused of negligence.[73] In a US study, approximately 9% of medical oncologists receive at least one complaint annually relating to negligence, a proportion in line with other disciplines, with the exception of surgery which is traditionally more exposed.[74] A similar survey on 4000 clinicians showed that male oncologists were more subject to persecution compared with females (37% vs 26%). Thirty per cent of male oncologists and 23% of female oncologists were cited for negligence together with other professionals. The main subjects of these conflicts were related to unexpected damages caused by procedures (34%), missed diagnosis (19%), refusal of treatments (14%), errors in the administration of drugs (10%), security procedures (8%) and insufficient documentation and/or information of the patient (5%). Finally, 34% of oncologists conclude that the CW initiative could increase the risk of being prosecuted, 28% of them do not think that this will happen and the remaining ones were undecided.[75] In a survey among Italian radio-oncologists, 39% ordered laboratory or radiological exams, 43% sent patients to another consultant and 35% prescribed additional treatment all in a defensive purpose.[76]

Often therapeutic decisions are taken during multidisciplinary meetings, during which several professionals give their contribution but only few of them have direct responsibility in the treatment of the patient. This can have potential implications from a legal point of view and on the application of futile diagnostic or therapeutic measures.[77]

Conflict of interest

Conflict of interest (CI) is frequent and because of technological evolution the oncology sector is particularly exposed. A study evaluated the importance of financial CI for 125 authors of the National Comprehensive Cancer Network (NCCN) guidelines. Eighty-six per cent of these authors declare to have at least one CI because of honoraria from industry,[78] it is not easy to understand to which point this involvement can have consequences on the guidelines. Similar proportions of financial CI were reported among 642 hemato-oncologists in the USA.[79] CI can have a potential impact in the development of research, for example, honoraria for consultancies and financing of research. A systematic review showed that approximately 1/4 of researchers are affiliated to industry. Besides, when analysing publications a statistically significant association was evident between sponsoring from the industry and conclusions favouring the product. Finally, industry sponsoring is correlated with obstacles in the diffusion and publication of data.[80] Even though it is recognised that a tight collaboration among biomedical researchers and industry have enhanced the development of new therapeutic frontiers,[81] the tight collaboration between academic researchers and industry opens the possibility of CI through development of non-ethical behaviours and the influence on the conduct of researches through scientific biases which can compromise the interest of the patients and the public. In a study based on autodeclaration, 40%–50% of oncologists without a fix salary declared to increase their revenues thanks to the administration of chemotherapy or growth factors.[82] That financial incentive is a potential CI is also shown by a further study in which 65% of the professionals' revenue was due to the administration of drugs.[83] These drugs were unfortunately not always used appropriately, as suggested by another study in which it was seen that the use of growth factors was prescribed in 96% of cases without considering the guidelines.[84] Another study points out that 58% of radio-oncologists received compensation from the industry, a proportion still inferior to the surgical oncologists (84%); finally, the medical oncologist received an even higher financing *pro capite* from the industry compared with the previous two categories.[85]

The major oncology societies (ASCO, ESMO, ASTRO and ASH) prepared guidelines to reduce the risk of CI in their employees involved in scientific activities, and in developing educational events (congresses) and products, publications or guidelines. In an analysis of 4219 abstracts including 28 283 authors, all the abstracts reported a declaration of CI, of which 13.4% with at least one CI; despite this, only 4.5% of authors declared a potential CI. The CI declarations were more frequently reported in US performed studies, compared with the studies performed in the rest of the world.[86]

Asking for donations from patients could also represent a potential CI? A survey among oncologists of comprehensive cancer centres of the National Cancer Institute revealed that 71% of them were invited by their own institute to help in fundraising, and 26% of them received information on ethical behaviour during this practice; interestingly, 74% of the participants admitted that this practice could interfere with the doctor/patient relationship and 52% considered that this could represent a CI.[87]

In conclusion, most of evidence regarding CI in cancer care arise from North America. It is difficult to translate these data to the European or Asian reality, because political and economic factors (including financial

attractiveness) are responsible for substantial differences in the CI issue among countries.

Choosing Wisely, economy and politics

The demographic increase and the ageing of the population has brought the cancer issue among the priorities of both the public and politicians, also because of its economic consequences while facing more and more limited resources. Costs are influenced by many factors, including the rapid expansion and accelerated renewal of technologies consequent to the growing research results, the lack of good health economy studies, the access disparity to technologies for the patients, the limits of the regulatory systems and, last but not least, the overuse of technologies.[88] What are the potential economic and political consequences of CW, or inversely, how much CW is conditioned by economy and politics? First of all, it must be taken into account that sanitary expenditures are quite different from country to country even in the high social economic level lands. Despite a yearly *pro capite* expenditure for cancer of approximately €100 larger in the USA compared with Europe, it is not sure if this difference results in a better patient treatment[89–91]; on the contrary, the outcomes appear to be similar if not even better in some European countries with more restrictive politics.[92] The recent economic recession has imposed austerity measures, and several European countries had to cut on health expenditures, resulting in less efficient services and less accessibility to new drugs.[93–95] The more striking example of political pressure in the sanitary environment is the National Institute for Health and Care Excellence (NICE) created to support the National Health Service in Great Britain to help it identify futile procedures in terms of cost-benefit relationship.[96] Plans like NICE are considered by many to be influenced by politics, technocracy and too much under administration control, and therefore too difficult to accept.

HOW TO PUT CW INTO PRACTICE?

Changing long-standing practice is challenging. Plans relying on an individual who must remember to make a change are doomed to fail; however, individual physicians can become leaders in building workflows and systems facilitating change, so that new habits become routine. The challenges to implement CW are likely different across oncology disciplines; as such, the solutions should be created locally to maximise buy-in and chance of success. Within single institutions, a multidisciplinary and multiprofessional team might also review the CW recommendations and choose one or two on which to base a quality-improvement project. Electronic health records could help the successful implementation of CW recommendations. For instance, electronic health records should take into account each patient's medical history so that alerts are triggered on prescriptions for patients meeting specific criteria. Responding to patients' requests on unnecessary interventions may be more challenging, but those conversations do not have to be handled only by physicians. Nurses, medical assistants and physician extenders can reinforce the message, especially in advanced lines of therapy for incurable diseases.

Lastly, undergraduate medical education needs to equip students with the foundations on which clinical reasoning skills can be acquired and fostered throughout their clinical career. Teaching these skills usually involves patients (eg, bedside teaching), but it could also be delivered in the format of formalised small-group, case-based learning.

CONCLUSIONS

Putting the patient at the centre of the process of care, the CW was developed by a multi-professional force promoted by medical doctors. Recommendations proposed by some of the most important oncology societies should be considered a starting point and a sensitivity signal in this movement from the oncological milieu. Nevertheless, the way to go is still long, especially if a real cultural change in the oncological community must happen before CW becomes a real *modus operandi*. This implies that every professional should get involved and the institutions and the medical associations should be in charge of the teaching. While respecting the medical autonomy and competences, it would be paramount to identify clinical situations in which abstention is better than treatment, and make this information available to the medical and non-medical public. The next step would be to develop interventional plans in order to maintain the use of appropriate care while discouraging the use of treatments with limited therapeutic impact, and finally to create models which could measure the impact of the applied strategies.[97]

Clearly there are potential flaws in the CW initiative, perhaps the biggest being the lack of uniform metrics. It is easy to assert that a test is unnecessary, but what criteria are used to reliably and prospectively define what is necessary? Failing to have a standard definition for 'unnecessary' medical care is bound to introduce immediate biases into the determination of a medical procedure utility. Of paramount importance, how can we improve quality when we haven't unanimously defined quality?

The most important challenge will probably be the change of attitude in clinical practice for the cases in which scientific evidence suggest that the proposed intervention has modest or no impact or could even be detrimental. This change is necessary and the challenge should be accepted quickly, so that CW more and more will mean *Choosing Right*.

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