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Critical Reviews in Oncology/Hematology xxx (2010) xxx–xxx

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

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Guidelines, minimal requirements and standard of cancer care around the Mediterranean Area: Report from the Collaborative AROME (Association of Radiotherapy and Oncology of the Mediterranean Area) working parties

AROME *,[1]

Accepted 24 March 2010

Contents

Abbreviations: ACR, American College of Radiology; AJCC, American Joint Committee on Cancer; BCG, Bacillus Calmette-Guerrain; BED, biologically equivalent dose; BCS, breast conserving surgery; BRCA, breast cancer gene; CEA, carcinoembryic antigen; ChemoT, chemotherapy; CISH, chromogenic in situ hybridisation; CDDP, cisplatin; CR, complete response/responder; CT, computed tomography; ENT, ear–nose–throat; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; FISH, fluorescence in situ hybridization; FOLFOX, 5 fluorouracil, leucovorin, oxaliplatin; Gy, Gray; HR, hormone-receptor; HT, hormone therapy; IHC, immunohistochemistry; IMRT, intensity modulated radiotherapy; LDH, lactate dehydrogenase; LH-RH, luteinizing hormone-releasing hormone; LV, lymphovascular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; M-VAC, methotrexate, vinblastine, doxorubicin, and cisplatin; m, month; N+, nodes positive; PCI, prophylactic cranial irradiation; PE, etoposide; PR, progesterone receptor; PS, performance status; PSA, prostatic specific antigen; q, every; RT, radiotherapy; RDE, rectal digital examination; SBR, Scarff–Bloom–Richardson; SLNB, sentinel nodde biopsy; TNM, tumor-node-metastasis staging system; TURBT, transurethral resection of the bladder tumor; UICC, Union International Contre le Cancer; u/s, ultrasound; WHO, World health Organization; y, year; 3D-CRT, three-dimensional; 2D-EBRT, two-dimensional external beam RT.

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1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2010.03.007

Please cite this article in press as: AROME . Guidelines, minimal requirements and standard of cancer care around the Mediterranean Area: Report from the Collaborative AROME (Association of Radiotherapy and Oncology of the Mediterranean Area) working parties. Crit Rev Oncol/Hematol (2010), doi:10.1016/j.critrevonc.2010.03.007

Abstract

Guidelines are produced in oncology to facilitate clinical decision making and improve clinical practice. However, existing guidelines are mainly developed for countries with a certain availability of means and cultural aspects are rarely taken into account. Around the Mediterranean Area, countries share common cultural backgrounds but also great disparities with respect to availability of means; current guidelines by most societies are not applicable to all of those countries. Association of Radiotherapy and Oncology of the Mediterranean Area (AROME) is a scientific organization for the promotion and overcoming of inequalities in oncology clinical practice around the Mediterranean Area. In an effort to accomplish this goal, members of the AROME society have developed clinical recommendations for most common cancer sites in countries around the Mediterranean Area. The structure of these recommendations lies in the concept of *minimal requirements* vs. *standard of care*; they are being presented and discussed in the main text.

Keywords: Guidelines; Recommendations; Cancer care; Mediterranean Area

1. Introduction

Diseases are rare in medicine charge as much fear of death and involving as many specialists as cancer care. However the main goal of cancer treatment is still curative. Because of the complexity of the strategy according to different factors as tumour stage, tumour biology, comorbidities but also economical and cultural aspects we need guidelines. A clinical practice guideline has been defined as: "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" Field and Lohr [1]. An enormous amount of publications appear every year to develop "guidelines" aiming to organize the abundant literature and to promote education and guidance to the oncologists in their decision making. The majority of these guidelines are performed by European and North American study groups addressing specific sites, stages and clinical situations without, however, considering specific availability of means.

This mainstay of treatment unfortunately cannot be achieved in the majority of countries globally, due to various reasons, such as socioeconomic conditions, limited education of involved professionals, inadaptability of a new modality due to the mentality or the cultural background of a given people, as well as lack of education for cancer prevention in a population. Finally, cancer incidence varies among different geographical areas in the world demanding a diverse adaptation of strategies against it and a distinct use of the available means. This is particularly true when countries around the Mediterranean Area (MA) are concerned [3–8].

More specifically, as far as the northern part of the MA is concerned, there are several socioeconomic discrepancies even among European countries; these are being clearly reflected to health issues and it is now known that adherence to guidelines is not uniform among European countries, not even among departments in the same country [9,10]. Furthermore, at the southern-eastern MA, cancer has not been recognized as a public health problem until the last 10 years in the countries of Northern Africa (Morocco, Tunisia, Algeria, Libya) and in the countries of Middle East (Egypt, Syria, Jordan, Lebanon); these countries had, until then, given priority to transmissible diseases [11]; a fact that has begun to change over the 80s, since the formation of national cancer registries in most of these countries [12–17].

2. Materials and methods

2.1. AROME concept

Association of Radiotherapy and Oncology of the Mediterranean Area (AROME; www.aromecancer.org) is a medical organization aiming the collaboration of oncologists and other health care professionals implied in cancer care working in the area. The scope of the Association is to recognize the special circumstances and issues in the MA, to discuss and acknowledge openly existing issues in order to improve the existing problems, with a special interest at overcoming disparities in cancer care by various actions. AROME's special focus is placed on the promotion of education and training in cancer care in implied professionals and the communities around the MA.

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2.2. Aims and scope of AROME guidelines

In that concept, in the first AROME meeting held in Naples in April 2007, oncologists around the MA met and presented epidemiologic data from their respective countries. This was the first step for the recognition of the specific epidemiologic characteristics in the area, followed by the next step of presenting and recognizing the availability of means to provide cancer care in the various countries. Ultimately it became evident that optimum means were not available in several countries, which led to the recognition of the fact that cancer care should be re-evaluated and guidelines for treating specific cancer sites should be revisited, since they are inapplicable for several countries in the area. As a second step of the concept, site-specific working groups consisting of oncologists from different disciplines and different countries of the MA were formed. During the second AROME meeting "AROME guidelines for cancer care around the Mediterranean Area" were generated according to a process of a formalized consensus.

These guidelines were structured in a basic way. It was decided that *Minimum requirements* should be proposed, consisting of the minimal actions any oncologist should be able to perform anywhere in order to provide the acceptable minimum cancer care. These guidelines aimed to form the basic level, and oncologists should recognize that it would be inappropriate to treat cancer patients without availability of these requirements. On the other hand they aimed to rationalize cancer care and make better management of the available means so as to treat more patients in a most cost-effective manner. Existing guidelines for optimum care in countries with limited resources proposed by organizations such as the International Atomic Energy Agency (IAEA), Breast Health Global Initiative (BHGI) [2,18–20] were also taken into account during the preparation of the recommendations for the MA.

Furthermore, the existing guidelines proposed by major societies for the countries with optimal resources around the MA were taken into account. Members of the panels tried however, to be more Mediterranean-needs oriented and to face routine situations in the Mediterranean countries as they were presented by AROME representatives. These guidelines aimed at stretching the need for political pressure by professionals to the respective governments; they aimed to become a useful tool for providing evidence that optimum care is achievable and to inspire pieces of action in this direction to increase the cancer care to a higher level. Moreover, they may serve as a baseline of optimum care in decision making by oncologists around the Mediterranean Area.

However, it cannot be emphasized enough that this meeting highlighted another important issue which these guidelines aim to underline: that the interdisciplinary approach and communication by the different specialists involved in cancer care is the most cost-effective strategy; it is free of charge, however it can lead to an organized decision making saving the patient a lot of useless discomfort and intervening at optimum timings with optimum medical actions.

These guidelines were composed of recommendations based on the best evidence available at the time of the meeting, as they were reviewed by members of the panel. Each panel comprised of 8–9 cancer specialists of various specialties: radiation oncologists, medical oncologists, surgical oncologists, physicians of nuclear medicine and epidemiologists. These guidelines aim to be updated at a *3 years* interval in order to include recent evidence-based study results, as well as the eventual progress in means in the limited resources countries, allowing for a shift from minimal to potentially standard of care guidelines. However, if a major evolution takes place for a given cancer site, "express" guidelines will be prepared at anytime by AROME panelists in order to include the latest change. It is crucial to confront these guidelines with the notion that they are dynamic documents, as already proposed by National Comprehensive Cancer Network (NCCN) for their respective guidelines [21]. AROME aims to include professionals from more disciplines involved in cancer care into the next guideline updates.

2.3. Manuscript writing

During the meeting in Istanbul, all the available scientific evidence concerning a specific disease site was presented by members of the panel and discussed upon. After the meeting, members of the panels communicated through e-mails and prepared the below presented tables and text, that were reviewed by the respective chairmen. The manuscript was prepared by several AROME representatives that had already participated in panels for different disease sites. The final manuscript was read and approved by all panel members and revisions were made after comments allowed to any member of the panel were received. Authors are currently active professionals in oncology in Mediterranean countries and might be considered experts in their field. No funding from the industry or participation of any of its representatives was allowed to ensure independence of guidelines development. No conflicts of interest exist for any member of the panel.

3. Results

3.1. Concept of minimal requirements vs. standard of care

As discussed in the manuscript "AROME epidemiology and means around the Mediterranean Area", which is currently being prepared for publication, most common cancers in the MA are: lung, breast, prostate, bladder, cervical, head and neck and colorectal cancer. Thereby follows a set of tables presenting the guidelines for every important disease entity around the MA. These guidelines focus on these major issues:

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Table 1
Guidelines for prostate cancer.

Minimum requirements	Standard of care
Screening	Screening
Patient asymptomatic > 50 years	Patient asymptomatic > 50 years
PSA q 2 y + RDE by urologist	PSA annualy + RDE by urologist
Symptomatic patient	Symptomatic patient
RDE	DRE
Total PSA	Total PSA
Endorectal ultrasound	Endorectal ultrasound
	TRUS-guided biopsy
Indications of biopsy	Indications of biopsy
Transrectal multiple biopsies done by urologist oriented by RDE	Biopsy under ultrasound (*TRUS-guided biopsy*)
Minimal number of 8 cores	*20 cores*
Conventional histopathologic examination-Gleason score	*IHC* in addition to conventional histopathology
Staging	Staging
Clinical examination	All the minimum
TNM classification	*MRI*
Gleason score	*PET scan* (*optional*)
Pelvic CT-scan	
Bone scintigraphy	
Treatment	Treatment
Localized (D'Amico's criteria)	Localized (D'Amico's criteria)
Low risk	Low risk
<70 years	<70 years
Prostatectomy	Prostatectomy
RT	3D-CRT (IMRT and brachytherapy: optional)
>70 years	>70 years
2D-EBRT	3D-CRT (IMRT and brachytherapy: optional)
Prostatectomy (optional) watch and wait	Prostatectomy (optional)
	Watch and wait
Intermediate	Intermediate
<70 years	<70 years
Prostatectomy	Prostatectomy
2D-EBRT + short HT	3D-CRT (optional IMRT) + short HT
70 years	70 years
2D-EBRT + short HT	3D-CRT (optional IMRT) + short HT
High risk	High risk
<70 years	<70 years
2D-EBRT + prolonged HT	3D-CRT (IMRT and brachytherapy: optional) + prolonged HT
Adjuvant HT after surgery (pN+)	Adjuvant HT after surgery (pN+)
Adjuvant 2D-EBRT after surgery (margins (+)/pT3 or pT4)	3D-CRT (optional IMRT) after surgery (margins (+)/pT3 or pT4)
>70 years	>70 years
2D-EBRT − HT	3D-CRT (IMRT and brachytherapy: optional) + HT
Locally advanced disease non-metastatic	Locally advanced disease non-metastatic
2D-EBRT + HT	3D-CRT (optional IMRT) + HT
Patients with positive nodes	Patients with positive nodes
Patients operated	Patients operated
HT	HT
Patients non operated	Patients non operated
2D-EBRT-HT	3D-CRT (optional IMRT)-HT
Treatment failures	Treatment failures
Rising PSA after prostatectomy	Rising PSA after prostatectomy
>0.2 ng/ml	>0.2 ng/ml
PSA doubling time > 6 months bone scintigraphy and pelvis CT-scan	PSA doubling time > 6 months
Clinical and/or radiological relapse	Bone scintigraphy and pelvis CT-scan
2D-EBRT-HT	*MRI*
Isolated PSA rising	Clinical and/or radiological relapse
HT	3D-CRT (optional IMRT)-HT
	Isolated PSA rising
	3D-CRT (optional IMRT)-HT
Metastatic disease	Metastatic disease
HT	HT

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Table 1 (*Continued*)

Minimum requirements	Standard of care
Palliative 2D-RT	Palliative RT *Metabolic therapy-chemoT*
Metastatic and locally advanced patients	Metastatic and locally advanced patients
Therapeutic window	Therapeutic window
Minimal initial treatment of 6–12 months of treatment until PSA decrease to <4 ng/ml	Minimal initial treatment of 6–12 months of treatment until PSA decrease to <4 ng/ml
Restart the treatment when PSA > 10 ng/ml	Restart the treatment when PSA > 10 ng/ml
Early retreatment reduce the rate of bone complications	Early retreatment reduce the rate of bone complications
Progression under HT	Progression under HT
2nd line HT (anti-androgen and LH-RH analogues)	2nd line HT (anti-androgen and LH-RH analogues)
Failure → chemoT	Failure → chemoT

- Prevention/screening when applicable.
- Diagnosis.
- Staging.
- Treatment.
- Follow-up.

Tables 1–7 outline briefly the proposed AROME *minimum requirements* vs. *standard of care*. Table 8 outlines the minimum *available means* necessary for the management of each disease site vs. the standard of care of available means. Herein follows a discussion of the main points that emerge from the tables, concerning each disease site.

3.2. Minimal requirements vs. standard of care in the main type of cancers around the Mediterranean Area

3.2.1. Prostate cancer

For diagnosis of prostate cancer, fewer cores are demanded for the biopsy specimen, since the biopsy is not being undertaken under ultrasound. No immunohistochemistry is demanded for the evaluation of the biopsy specimen for a minimum care. No magnetic resonance imaging (MRI) is available everywhere to provide minimum acceptable care regarding staging. All this information will not adequately stage the patient as for treatment decisions. Conformal radiotherapy (RT), chemotherapy for hormonoresistant patients, ablatherapy, metabolic therapy or colieoscopic surgery are necessary as minimum treatment but not available everywhere. It is questionable however, if the minimum requirement of hormone therapy can be available to every patient with prostate cancer. In our mind, the most important of these limitations is the unavailability of conformal RT, which does not allow for dose escalation, a treatment feature that has proved essential for optimization of prostate cancer care. Therefore, we believe that prompt clinical examination with rectal digital examination, PSA measurements, biopsies taken and conventional histopathology, will allow for treatment of prostate cancer with prostatectomy, RT or hormone therapy, provided availability of drugs and essential RT machines (simulator and linear accelerator) exist. This would be the minimal requirements for a center to be allowed to take care of prostate cancer anywhere in the world.

3.2.2. Bladder cancer

Cystoscopy urine cytology and the possibility to perform a CT-scan at least of the pelvis and biopsies are adequate to stage the patient. Concerning treatment the ability to perform transurethral resection or intravesical instillations or even more selective cystectomy techniques combined with chemoradiotherapy would almost lead to optimal treatment. However, when no supportive units are available for concomitant radiochemotherapy and no BCG or chemotherapy instillations are available, the ability to perform cystectomy is of ominous importance and would serve as a basis of minimal requirement.

3.2.3. Lung cancer

In lung cancer minimal requirements do not demand the use of fluorodesoxyglucose PET or mediastinoscopy for exclusion of unresectability. However, one must bear in mind that CT-scan alone is inadequate for staging and that absence of these means will lead to an increased number of unnecessary thoracotomies. However, the absence of conformal RT for dose escalation, or hospitalization units to allow for supportive care and make concomitant chemoradiotherapy possible is the two main limitations with the adoption of minimum guidelines, as well as the inability to exclude preoperatively the unresectable patients. The use of more hypofractionated regimens when RT is offered as sole modality, will lead to the sparing of resources when the scope of the intervention is, as in most cases mostly palliative.

3.2.4. Breast cancer

In breast cancer, for early detection screening mammography cannot be proposed as a minimum requirement for MA. Public awareness and breast self examination are recommended. For the diagnosis and pathological reporting immunohistochemistry, reporting of lymphovascular invasion and sentinel node biopsy is not required. Mastectomy should be proposed as the surgical technique when RT is not available.

For follow-up, systematic pelvic ultrasound in women receiving tamoxifen, bone mineral density and left ventricular ejection fraction examinations are essential. We believe

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Table 2
Bladder cancer.

Minimum requirements	Standard of care
For initial work-up in bladder cancer Clinical examination Cystoscopy Biopsies Pelvic CT-scan Urine cytology Bone scintigraphy	For Initial work-up in bladder cancer Clinical examination Cystoscopy Biopsies (*mapping biopsies including TUR biopsy of the prostate*) Pelvic and *chest CT*-scan Urine cytology Bone scintigraphy
Treatment Carcinoma in situ (TIS/Ta/T1) (N0M0) TURB Single dose intravesical chemoT (BCG or mitomycin)	Treatment Carcinoma in situ (TIS/Ta/T1) (N0M0) *Examination under anesthesia* TURB Single dose intravesical chemoT (BCG or mitomycin)
Localized bladder cancer (T2 high grade, T3a) Radical cystectomy Possibly also: ±neoadjuvant cisplatin based chemoT ± adjuvant cisplatin based chemoT (if no neoadjuvant) RT + CT (concomitant if supportive care available)	Localized bladder cancer (T2 high grade, T3a) Radical cystectomy ± neoadjuvant cisplatin based chemoT ± adjuvant cisplatin based chemoT (if no neoadjuvant) or segmental cystectomy ± neoadjuvant cisplatin based chemotherapy ± adjuvant RT + cisplatin based chemotherapy (if no neo adjuvant) or *selective bladder sparing after maximal TURBT* (if no hydronephrosis) after neoadjuvant RT + chemoT or RT + CT
Bladder cancer node positive, M0 Preoperative N+ Primary chemoT Responders → secondary surgery Non responders → secondary surgery or RT + chemoT	Bladder cancer node positive, M0 Preoperative N+ ChemoT + RT → evaluation with cystoscopy No tumor: follow-up or boost (RT) or surgery Residual disease: cystectomy, or RT (if not prior), or palliative TURBT
Primary surgery → node positive Bladder cancer node positive after surgery Adjuvant chemoT without proved benefit No indication of adjuvant RT excluding epidermoid type	Primary surgery → node positive Bladder cancer node positive after surgery Adjuvant chemoT without proved benefit No indication of adjuvant RT excluding epidermoid type
Bladder cancer node positive RT + chemoT	Bladder cancer node positive RT + chemoT
Metastatic patients Systemic palliative chemoT (M-VAC) or cisplatin-gemcitabin Palliative chemoT Palliative RT Supportive care	Metastatic patients Systemic palliative chemoT (M-VAC) or cisplatin-gemcitabin Palliative chemoT Palliative RT Supportive care

that among the limitations of the minimal requirements, the most important is the absence of an organized mammographic screening for all women. Concerning treatment, it has provocatively been mentioned that when resources are really scarce, the only cost-effective strategy is surgery, which might be true in terms of economic definitions, however, around the MA we believe that there is availability of at least tamoxifen as adjuvant modality [22].

3.2.5. Carcinoma of the cervix

For cervival cancer, no colposcopy and no MRI and/or CT-scan are a prerequisite of diagnosis, while no lymphovascular invasion should be routinely reported in pathologic examinations. In treatment, no brachytherapy availability and no para-aortic lymph node dissection are minimal requirements, while no CT or MRI scans or clinical trials access is essential as a minimum requirement for follow-up. We believe that the vaccination issue as well as the gynecologic examination under general anesthesia is important issues to be reflected upon that are missing from the minimum requirements. Although the vaccination cost is expected to be too much for vaccination to be offered in every limited resource country, one must bear in mind that cervical cancer is very common around the MA and the implementation of vaccination might actually prove cost-effective even by strict economic standards.

3.2.6. Head and neck cancer

No MRI, PET or PET/CT-scan, no panendoscopy and no assessement of Epstein-Barr virus (EBV) are a prerequisite of minimal guidelines for establishing a diagnosis. Moreover, no conformal RT, no taxane chemotherapy or endothelial growth factor receptor (EGFR) targeted therapy are an essential component of minimum treatment. We believe that the absence of conformal RT and targeted treatments is a limitation of the therapeutic potential of minimum guidelines. However,

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Table 3
Lung cancer.

Minimum requirements	Standard of care
Diagnosis	Diagnosis
Exclude unresectability by	Exclude unresectability by
Clinical examination	Chest X-ray + CT (liver + adrenals included)
Chest X-ray	*FDG-PET*
Liver function tests and liver US	*Mediastinoscopy*
Bone scan only if clinical indications	*Biopsy through bronchoscopy or CT guidance*
CT (or MRI) of brain only if limited disease	
Above results + PS + serum sodium and LDH to assess the patient's likely prognosis	
Treatment	Treatment
Stage I	Stage I
Surgical resection	Surgical resection
Postoperative treatment	Postoperative treatment
IA (T1N0)	IA (T1N0)
Margins (−): observe or chemoT in high risk patients	Margins (−): observe or chemoT in high risk patients
Margins (+): RT	Margins (+): *reresection* or RT
IB (T2N0)	IB (T2N0)
Margins (−): chemoT	Margins (−): chemoT
Margins (+): RT + chemoT	Margins (+): *reresection* RT + chemoT concommitantly
Stage I: medically inoperable patients	Stage I: medically inoperable patients
Curative RT	Curative RT
Small tumours hypofractionated regimen	3D Conformal RT
	Stereotactic RT with BED of at least 100 Gy
Stage II: favorable IIIA	Stage II: favorable IIIA
Surgical resection	Surgical resection
Postoperative treatment	Postoperative treatment
IIA, favorable IIB (T1-2N1)	IIA, favorable IIB (T1-2N1)
Margins (−): chemoT, or chemoT + RT if adverse factors	Margins (−): chemoT, or chemoT + RT if adverse factors
Margins (+): chemoT or RT + chemoT	Margins (+): *reresection* or chemoT or RT + chemoT
Favorable IIIA (T1-2N2)	Favorable IIIA (T1-2N2)
Margins (−): chemoT or RT + chemoT	Margins (−): chemoT or RT + chemoT
Margins (+): RT + chemoT concomitantly	Margins (+): *reresection* or RT + chemoT concomitantly
NSCLC stage IIIA-B (unfavorable)	NSCLC stage IIIA-B (unfavorable)
T3-4, N1 superious sulcus tumor	T3-4, N1 superious sulcus tumor
Resectable: chemoT + RT (concomitant if possible) followed by surgery	Resectable: chemoT + RT (concomitant) followed by surgery
Marginally resectable: chemoT + RT (concomitant if possible) followed by evaluation and surgery or if unresectable definitive RT + chemoT	Marginally resectable: chemoT + RT (concomitant) followed by evaluation and surgery or if unresectable definitive RT + CT
Unresectable: chemoT + RT concomitantly if possible	Unresectable: chemoT + RT concomitantly
Chest wall T3N1: surgery or RT or chemoT or RT + chemoT concomitant if possible	Chest wall T3N1: surgery or RT or chemoT or RT + chemoT concomitant
IIIA: T3N2: unresectable	IIIA: T3N2: unresectable
chemoT + RT concomitantly if possible	chemoT + RT concomitantly if possible
IIIB: T4N1: surgery followed by chemoT	IIIB: T4N1: surgery followed by chemoT
T3N3: chemoT + RT concomitantly followed by consolidation chemoT	T3N3: chemoT + RT concomitantly followed by consolidation chemoT
	ChemoT + RT concomitantly followed by consolidation chemoT
Stage IV (metastatic disease)	Stage IV (metastatic disease)
ChemoT if PS: 0–2	ChemoT if PS: 0–2
2 drugs combination	2 drugs combination
CDDP with older drugs	Platinum or non-platinum-based
CDDP with 2nd or 3rd generation agents if available	<6 cycles, <4 if no response
<6 cycles, <4 if no response	As soon as possible (good PS)
As soon as possible (good PS)	Elderly: 1 drug
Elderly: 1 drug	2nd line CT if PS, DF interval good: docetaxel
Supportive care	3rd line: gefitinib
	Investigational agents, 2 cycles, if PD, cross over
Follow-up	Follow-up
History/physical examination	History/physical examination
Every 3 m first 2 y	Every 3 m first 2 y

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Table 3 (*Continued*)

Minimum requirements	Standard of care
Every 6 m 2–5 y Every 1 y thereafter Chest radiographs: no Other diagnostic procedures: no, unless symptomatic patient	Every 6 m 2–5 y Every 1 y thereafter Chest radiographs: no Other diagnostic procedures: no, unless symptomatic patient
SCLC staging As in NSCLC	*SCLC staging* *CT chest ± upper abdomen*, hematological tests *Bone scan, brain CT, bone marrow biopsy*: when patient symptomatic
SCLC treatment Limited disease CDDP and etoposide (PE) Consolidation RT after Concurrent RT and CT PCI in CRs and good PRs	SCLC treatment Limited disease *Concurrent* chemoT+ RT with CDDP-etoposide *3D conformal RT* *IMRT* *RT gating* PCI in CRs and good PRs
Extensive disease ChemoT: same regimens as for limited disease Second-line chemoT Response evaluation is recommended at least at the end of treatment by repetition of the initial radiographic tests Follow-up: no follow-up of asymptomatic patients	ChemoT palliative RT for palliation or in place of chemoT PCI for good responders

the most cost-effective strategy would certainly be the smoking cessation campaigns as well as limitation of alcohol use around the MA, which would limit considerably the incidence of head and neck cancer.

3.2.7. Colorectal cancer

For colorectal cancer, no organized national screening, no coloscopy as part of the screening procedure and no oncogenetic counseling for people bearing familial risk are essential for minimum preventive care. No CT, no PET, no carcinoembriyic antigen (CEA) detection are essential parts of minimum diagnosis. This is also true for follow-up. For treatment, we believe that the absence of appropriate staging by CT or endorectal ultrasound before treatment decision and the unavailability of drugs such as oxaliplatin limit the chance of cure in the minimum guidelines.

4. Discussion

The Mediterranean has been the sea that has given birth to what is called today "the western civilization". Various ancient or more recent people that have long interplayed with each other clearly share many common features concerning lifestyles, cultures and mentalities. On the other hand, there is a great disparity of socioeconomic structures among the countries surrounding the MA, which limits the possibility of cancer care uniformisation [23]. For instance, on the one hand, there are Mediterranean countries, such as Spain, Italy and Greece which are relatively wealthy and present cancer survival rates that are superior to those of northern European countries. This can be attributed to many reasons, most important of which seems to be the Mediterranean diet [23–27]. On the other hand, there are countries of North Africa and the Eastern Mediterranean Region (EMR) that have among the lowest cancer survival rates in the world, although they sustain, as well, more or less the same mediaterranean diet [28,29]. This is obviously due to the lack of education, the lack of organized cancer care and limited resources.

Data are striking. The relative 5-year survival rates for breast cancer range from 80% or higher in North America to 38.8% Algeria, while in Italy and France survival rates range from 70% to 79% [30]. For colon cancer, the relative 5-year survival is approximately 60% in North America and 40% or lower in Algeria, while in Spain and France it ranges from 54% to 57%. The rates of survival for prostate cancer are 92% in the United States and less than 40% in Algeria [30].

At this point, one should acknowledge the lack of publications in the field and even the lack of formal national (or only regional) cancer registries in several countries. Therefore, before discussing this work, it is important to highlight the relative lack of evidence and also the fact that personal experiences from professionals currently working in the area were taken into serious account. One could argue that this is not a totally evidence-based, but also an opinion-based report and this is not completely wrong, as the lack of publications for the description of the exact situation in many among the countries of interest made it imperative that some personal opinions of oncologists practicing in these countries gained special attention and were thoroughly discussed among the working parties.

The purposes of clinical practice guidelines are to improve the quality of patient care (namely survival and quality of life) and assist clinical decisions by rationalizing the use of available resources and prioritizing research goals [3,31]. Guidelines have proven to be efficient in patient outcomes, at least in industrialized countries and tools to standardize guidelines have been developed [32–39]. Heterogeneity in

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Table 4
Breast cancer.

Minimum requirements	Standard of care
Primary prevention in BRCA mutated patients Ovarian ablation to consider regarding the parity	Primary prevention in BRCA mutated patients Ovarian ablation to consider regarding the parity
Secondary prevention/early detection Aware women and general practitioner about the risk of breast cancer and educate about clinical breast examination	Secondary prevention Organized *screening* mammography for every women after age of 50 every 2 years *Systematic mammography yearly* for the patient with *previous treated breast cancer* *Patient with high risk* and *followed in specialized centers*
Mammography quality criteria At least 2 orthogonal incidences ACR classification Systematic comparison in case of previous mammography ACR guidelines	Mammography quality criteria At least 2 orthogonal incidences ACR classification Systematic comparison in case of previous mammography ACR guidelines
Diagnosis Pathology confirming the diagnosis of cancer (positive cytology acceptable) Clinical breast examination Imaging (preferentially mammography, if not available U/S)	Diagnosis Pathology (*surgery or guided biopsy*) Clinical breast examination Mammography *and* U/S
Staging Pathologic reporting Malignancy and type Invasiveness SBR, grade pT pN Margins (+ or −) Conserve primary tumor 10 years minimum	Staging Pathologic reporting Malignancy and type Invasiveness SBR grade pT pN Margins (+ or −) Conserve primary tumor 10 years minimum *IHC for HER2 (FISH or CISH if needed), ER, PgR* *IHC for SLNB* *LV invasion*
Initial work-up after pathology results Gynecological examination According to clinical examination	Initial work-up after pathology results Gynecological examination According to clinical examination *According to pathological results* *Stage I: no systematic work-up* *Stage II-III: Bone, Thoracic and abdominal imaging* *Cardiac, liver and hematological function in case of chemotherapy*
Primary treatment decision T0–T3 mastectomy with axillary clearance or when at least 2D-EBRT available: BCS + RT T4d and/or N2 begin with systemic treatment T4 a, b, c begin with local treatment and do axillary clearence in case of surgery	Primary treatment decision T0–T3 mastectomy or BCS + RT Axillary clearance or *SLNB if T0–T1 and N0* T4d begin with chemoT T4 a, b, c and/or N2 begin with systemic treatment and do axillary clearence in case of surgery
Surgery quality control Macroscopic complete excision of the cancer In case of BCS cancer excision from the skin to pectoralis muscle Lumpectomy piece oriented for pathologist Optimal axillary dissection with aim to be informative (min 6 lymph nodes in the axillary specimen)	Surgery quality control ALL THE MINIMAL *Choice of surgical technique* (lumpectomy or mastectomy) *Clips to guide radiotherapists* in case of boost *SLN procedure* *Specialized oncology surgeon* for breast
Adjuvant treatment strategies 2D-EBRT in case of BCS or pN+ after mastectomy Tamoxifen for 5 years for all patients in case of unknown or positive hormone receptor	Adjuvant treatment strategies *Multidisciplinary approach* 2D/3D-EBRT of BCS or pN+ after mastectomy Tamoxifen for 5 years for all patients in case of unknown or positive hormone receptor if not menopaused

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Table 4 (*Continued*)

Minimum requirements	Standard of care
PolychemoT regimens containing cyclophosphamide and doxorubicine (in case of no cardiac dysfunction) are recommended for pN+ or pN0 and HR− (if you have the information). Minimum: 4 cycles Trastuzumab for 1 year in case of HER2+ patients (if HER2 status was tested)	Antihormonal treatment containing *aromatase inhibitors* independently of the strategy (upfront, sequential or extended). Menopausal status is initially defined before any chemotherapy PolychemoT regimens containing cyclophosphamide and doxorubicin (in case of no cardiac dysfunction) are recommended for pN0, HER2− and HR−. The number of cycles are 4–6 PolychemoT regimens containing *taxane*, cyclophosphamide and doxorubicin (in case of no cardiac dysfunction) are recommended for pN+ or pN0 and HER2+. The number of cycles are 6–8 Trastuzumab for 1 year in case of HER2+ patients
Follow-up concerning the cancer	Follow-up concerning the cancer
Clinical exam: every 6 months the first 2 years, then every year	Clinical exam: *every 3 months* the first year, then every 6 months for 2 years more, then every year
Mammography: every year	Mammography: every year
Follow-up concerning the cancer treatment	Follow-up concerning the cancer treatment
Clinical exam: every 6 months the first 2 years, then every year	Clinical exam: *every 3 months* the first year, then every 6 months for 2 years more, then every year
Gynecologic examination (if tamoxifen treatment)	*Transvaginal US* in case of gynecological symptoms *Bone mineral density* at the beginning *LVEF* to be considered for patients who will receive anthracyclines and/or trastuzumab and/or RT for left sided breast cancer

Table 5
Cervical cancer.

Minimum requirements	Standard of care
Prevention	Prevention
Organized screening	*Vaccination* and organized screening
Sexual education	Sexual education
Organized screening	Organized screening
Individual invitation to the women	Individual invitation to the women
Control of quality of the test	Control of quality of the test
Quality insurance for follow-up and treatment of the positive test	Quality insurance for follow-up and treatment of the positive test
Data collection	Data collection *and link with cancer registry*
WHO	WHO
Diagnosis and preclinical staging	Diagnosis and preclinical staging
Pathology (biopsy)	Pathology (biopsy)
Gynecologic examination	Gynecologic examination *under anesthesia in presence of surgeon and radiotherapist*
Abdomino pelvic US	*Colposcopy* in case of occult disease
Chest X-ray	*Abdominal CT-scan*
FIGO classification	Chest X-ray
	Pelvic CT-scan or MRI if available
	FIGO classification
Staging	Staging
Pathologic reporting	Pathologic reporting
Malignancy and type	Malignancy and type
Stromal invasion	Stromal invasion
Grade	Grade
pT	pT
pN	pN
Margins (+ or −)	Margins (+ or −)
	LV invasion
Primary treatment decision	Primary treatment decision
Multidisciplinary (surgeon, radiotherapist)	Multidisciplinary (surgeon, radiotherapist, *radiologist, medical oncologist*)
Operable (until IIa)	Operable (until IIa)

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Table 5 (*Continued*)

Minimum requirements	Standard of care
Surgery first and additional therapy depending of pTpN	Surgery *eventually after brachytherapy* and additional therapy depending of pTpN
Inoperable (IIb-IV)	Inoperable (IIb-IV)
Concomitant RT + chemoT (platinum-based) and additional therapy depending on response	Concomitant RT + chemoT (platinum-based) and additional therapy depending on response
Surgery quality control	Surgery quality control
Wertheim	Wertheim
Pelvic lymphadenectomy	Pelvic lymphadenectomy *and if positive para-aortic lymph nodes dissection*
Quality control in complete excision	Quality control in complete excision
Second step treatment	Second step treatment
Operated	Operated
Postoperative 2D-EBRT in case of deep cervical invasion and/or pN+ (with concomitant platinum-based chemoT)	Postoperative 2 or 3D-EBRT in case of deep cervical invasion and/or pN+ (with concomitant platinum-based chemoT)
Postoperative brachytherapy if margins (+) and/or parametrial invasion	Postoperative brachytherapy if margins (+) and/or parametrial invasion
Not operated	Not operated
Not responders: no recommendations	Not responders: no recommendations
Responders: surgery and/or brachytherapy	Responders: surgery and/or brachytherapy
Follow-up concerning the cancer	Follow-up concerning the cancer
Clinical and gynecological exam: every 3 months for the first 2 years, then every 6 months for 2 years, then yearly	Clinical and gynecological exam: every 3 months for the first 2 years, then every 6 months for 2 years, then yearly
Vaginal smear	Vaginal smear
Abdominal and pelvic US every 6 months the first 3 years	Abdominal and pelvic US every 6 months the first 3 years
Chest X-ray if symptoms	If positive US, *abdominal CT-scan and pelvic CT-scan or MRI every year*
	Chest X-ray if symptoms
Follow-up concerning the cancer treatment	Follow-up concerning the cancer treatment
Clinical and gynecological exam: every 3 months for the first 2 years, then every 6 months for 2 years, then yearly	Clinical and gynecological exam: every 3 for months the first 2 years, then every 6 months for 2 years, then yearly
Renal function (glomerular filtration) in case of cisplatinum-based chemotherapy	Renal function (glomerular filtration) in case of cisplatinum-based chemotherapy

Table 6
Head and neck cancer.

Minimum requirements	Standard of care
Diagnosis	Diagnosis
Patient should be examined by a head and neck surgeon	Patient should be examined by a *multidisciplinary team*
Imaging for loco regional and systemic work-up: CT	Imaging for locoregional and systemic work-up: CT, *MRI and PET or PET/CT*
Biopsy "primary or nodal"	*Panendoscopy and biopsy "primary or nodal" including IHC and immuno-phenotyping*
TNM staging according to latest AJCC/UICC staging systems	TNM staging according to latest AJCC/UICC staging systems
Dental assessment	Dental assessment
Nutritional and general health assessment by a medical doctor	Nutritional by and *nutritional specialist* and general health assessment by a medical doctor.
	In nasopharyngeal cancer EBV assessement before treatment and during follow-up.
Metastatic disease	Metastatic disease
Palliative treatment with medical and nutritional support	Palliative treatment with medical and nutritional support
Follow-up	Follow-up
Clinical ENT examination	Clinical ENT examination
Every 2/3 months for the first 2 years	Every 2/3 months for the first 2 years
Every 6 months until 5 years	Every 6 months until 5 years
Yearly thereafter	Yearly thereafter

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Table 7
Colorectal cancer.

Minimum requirements	Standard of care
Colon cancer	Colon cancer
Diagnosis	Diagnosis
Prevention	Prevention
Media campagnes educating on healthy diet, physical activity and healthy way of life in general	*Nationally organized screening program*
	Implications of different factors of public health and their associations
Treatment	Treatment
Stage: non-metastatic disease	Stage: non-metastatic disease
Surgery without any delay	Surgery *within 15 days* after work-up
At least 8 analysed nodes on pathologic report	Choice between *laparoscopy or laparotomy* according to the surgeon's pratice
Minimal margin: 5 cm	
Stage: non-synchronous metastatic disease	Stage: non-synchronous metastatic disease
Resectable	Resectable
Easily class1 surgery with or without peri operative chemoT	Easily class1 surgery with or without peri operative FOLFOX
Non-easily class 2: preopative chemoT	Non-easily class 2: preopative chemoT
	PET scan in the work-up
	Perioperative US
	Radiofrequency accessibility
Non-resectable metastatic disease	Non-resectable
5FU-based chemotherapy	Access at *all the effective drugs including targeted therapies*
In all cases miltidisciplinary decision is necessary	
Follow-up	Follow-up
Clinical examination every 3–6 months	Clinical examination every 3–6 months
Abdominal US every 3–6 months	Abdominal US every 3–6 months
Chest X-ray every year	Chest X-ray every year
Coloscopy at 3 years (1 year if preoperative incomplete coloscopy)	Coloscopy at 3 years (1 year if preoperative incomplete coloscopy)
	CEA monitoring
	CT body scan
	PET scan if elevated CEA $\geq$ *25%*
Rectal cancer	Rectal cancer
Staging-operability	Staging-operability
Digital examination	Digital examination
Coloscopy	Coloscopy
Body CT-scan	Body CT-scan
	Endorectal US
	Pelvic MRI
Treatment	Treatment
T1–T2 surgery alone	T1–T2 surgery alone
T3–T4 preoperative RT (no Cobalt)	T3–T4 preoperative RT (no cobalt)
Short delay	Short delay
Surgery 3–8 weeks after RT	Surgery 3–8 weeks after RT
	ChemoT $\pm$ *RT*
	Decision based on EER and/or MRI

guideline development is controversially seen: while some think it is a draw back to the uniformity of cancer patient care, our group believes that such heterogeneity is necessary if countries with limited resources or diverse cultures are to be taken into account. Other investigators agree and promote guideline flexibility as a necessary characteristic for meeting distinct needs [40–42].

Existing international guidelines address circumstances in countries where a certain wealth exists; moreover, they address the needs of people living mainly in northern Europe or northern America, that have a distinct socio-cultural issue from those of the MA. Adherence to these guidelines can be measured, as shown by ASCO/NCCN measures, for instance [43].

Guidelines intend to have implications in making treatment decisions with an impact on the patient–physician relationship. However, the intrinsic cultural and religious beliefs and the level of education of the patients can vary significantly in the MA. Therefore, existing "western" guidelines cannot be directly adopted by most countries of the MA. Some recent publications have addressed the issue of developing guidelines for countries with limited resources [2,19–21,44–49]. These can be valuable tools for physicians working in such countries, since they acknowledge

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Table 8
Minimum requirements of *available means* vs. standard of care.

Minimum requirements	Standard of care
Prostate cancer	Prostate cancer
Availability of treatment modalities	Availability of treatment modalities
LH-RH analogues	LH-RH analogues
Anti-androgens	Anti-androgens
Biphosphonates	Biphosphonates
Prostatectomy plus node dissection	Prostatectomy plus node dissection
Conventional radiotherapy (RT) (Cobalt)	Conformal RT
Conventional simulator	ChemoT for hormonoresistant patients
	Ablathermy
	Coelioscopic surgery
	Metabolic therapy
Bladder cancer	Bladder cancer
TURBT	TURBT
BCG therapy for 1 year	BCG therapy for 1 year
Cystectomy ± prostatectomy	Cystectomy ± prostatectomy
Lymph node dissection	Lymph node dissection
No defined number of nodes	No defined number of nodes
RT	RT + chemoT concomitantly
ChemoT (cisplatin-based)	
Lung cancer	Lung cancer
Diagnosis: radiograph, u/s, CT, bronchoscopy, histopatholgy laboratory	Diagnosis: radiograph, u/s, CT, bronchoscopy, histopatholgy laboratory,plus MRI, PET-CT (optimum care), mediastinoscopy
Treatment	Treatment
ChemoT: outpatient unit, cisplatin, etoposide availability	ChemoT: outpatient unit, cisplatin, etoposide availability plus: 2nd line or 3rd line agents
RT: conventional 2D simulator, cobalt unit	RT: 3D simulator, linear accelerator plus: IMRT, RT gating
Breast cancer	Breast cancer
Quality of breast cancer care organizations	Quality of breast cancer care organizations
Oncology team have to participate to quality control programs	Oncology team (epidemiologist, surgeon, radiotherapist, pathologist, radiologist, medical oncologist, nurses, supportive care, psychologs) have to participate to quality control programs
Give to patients information concerning diagnosis and treatment according to the standards of care of the unit	Give to patients information concerning diagnosis and treatment according to the standards of care of the unit
Access to supportive care and optimal analgesia in case of pain.	Access to *clinical trials*
Cervical cancer	Cervical cancer
Quality of cervix cancer care organizations	Quality of cervix cancer care organizations
Oncology team have to participate to quality control programs	Oncology team (epidemiologist, gynecologist, surgeon, radiotherapist, pathologist, radiologist, medical oncologist, nurses, supportive care, psychologs) have to participate to quality control programs
Give to patients information concerning diagnosis and treatment according to the standards of care of the unit	Give to patients information concerning diagnosis and treatment according to the standards of care of the unit
Access to supportive care and optimal analgesia in case of pain	Access to clinical trials

their needs more openly and offer practical suggestions for the optimum way to treat a patient regarding availability of means.

To our knowledge, the only published guidelines for limited resource countries concern breast and lung cancer [2,19–21,44–49]. These guidelines were read carefully by members of our panels and were adapted to the needs of the Mediterranean countries, according to the panelists' opinion. Interestingly, members of our panel have participated in these previously mentioned panels for the development of guidelines in limited resources countries. These guidelines are a first important step in the way of acknowledging the importance of adapting guidelines' to the availability of resources [50–52].

Inequalities in the MA include the different socioeconomic status between countries such as Spain or Italy to countries such as Egypt, the Palestinian authority or Algeria. Among rich countries, there is little correlation between gross national product (GNP) per person and life expectancy. Greece for example, with a GNP of US$17,000, has a life expectancy of 78.1 years; the USA, with a GNP $34,000, has a life expectancy of 76.9 years. Very often, populations with similar but restricted incomes present strikingly different health records; therefore the social gradient in health is a particular challenge [53,54].

Efforts by major organizations have already been made for ameliorating the situation in limited resources countries. WHO's cancer control programmes in the EMR have focused

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on developing programs and support to countries for setting up their own cancer registries, in a region where the main reasons for the recent increase in cancer-related mortality are increasing tobacco use; higher life expectancy and changes in lifestyle-particularly diet [55]. Only 50% of EMR countries have cancer control plans and major gaps in national capacity to prevent, detect, and manage cancer in the EMR exist, while national guidelines for the clinical management of common cancers are available in one third of these countries [55].

Another issue is the lack of access to cost-effective anticancer drugs, which are available in most northern countries, yet not affordable in more than 50% of the EMR, as well as the lack of good quality cancer data that poses obstacles to the formation of an evidence-based policy formation; most of the cancer data being derived from hospital-based registries (55). Combating the tobacco epidemics is a priority to WHO, with health education in school being pivotal for this issue, while other challenges include the establishment of cancer surveillance systems, primary prevention programmes, and the availability of optimal standards for the management and palliation of common cancers [55,56].

The purpose of the AROME guidelines is to bring to light the vast spectrum of possible practices adopted in the MA, to trigger conversation, to serve as a useful tool for any professional dealing with cancer in the area and to promote a multidisciplinary, cost-effective up-to-date management of cancer in the region. As already discussed, AROME guidelines do not aim to "teach" or "instruct" professionals in the MA. They aim to form a basis for the development of practices and policies leading from the *minimum requirements* to grow to the *standard of care*. However, their penetrance through the Mediterranean populations remains to be seen.

These *minimum requirements* provide a baseline for the best implementation of scarce resources to cancer care. On the other hand, they should not be seen by any means as competent. These guidelines aim to be updated due to the eventual amelioration of available means and the purpose of AROME is that someday they will coincide with *standard of care* in all countries around the MA.

However, this demands a great deal of political will, cooperation and organization of resources. The purpose of AROME is to become a tool for public pressure for the homogenization of resources around the MA, through educational interventions to health professionals and to the public and eventually the taking of political stands for optimization of the available means and the implementation of new techniques and technologies in countries around the MA.

The development of health systems and relief of poverty means taking action on the social determinants of health [54]. Health status should be of concern to all policy makers, not merely those within the health sector, because as underlined by Marmot M: "if health of a population suffers it is an indicator that the set of social arrangements needs to change" [55]. This is especially important because, in many countries, inequalities in health have been increasing [56–59]. The development of evidence-based policies, mobilization and appropriate allocation of resources, government commitment to legislation, education and international collaboration will eventually bring a more uniform health situation across the MA [24].

Initiatives in this direction have already been taken by the World Health Organization's STEPwise programme [60], by the International Atomic Energy Agency's PACT programme [61], the Global Summit Treatment and Allocation of Resources Panel and Breast Health Global Initiative [2], the WHO Framework Convention for Tobacco Control (WHO FCTC) [62]. Moreover, the Commission on Social Determinants of Health examines inequalities in health between countries and inequalities within [54]. At this point, it should be underlined that AROME is currently working in close collaboration with international organisations of cancer care and is aiming to strengthen these collaborations, a way to overcome the disparities and avoid duplication of efforts.

5. Conclusions

Governments must take public concerns about cancer seriously [63]. Collecting sound data and aligning cancer registries with international standards is an urgent public health demand. Screening through national initiatives, peoples' education and prevention, early diagnosis and decent cancer treatment are a realistic goal. As underlined by the Commission on Social Determinants of Health, it is challenging to convince policy makers that the health of the population is important because it is a measure of whether a population is benefiting as a result of a set of social arrangements [54]. Therefore, such improvement will indicate that society has moved in a direction of meeting human needs [64]. AROME "minimal requirements and standard of care" aimed to meet the distinct needs of the health systems of the countries around the MA, as well as the specific demands of patients and health professionals within them. In some countries such document that point out on "minimal requirement to treat patients" could be a mean of pressure on the local politics to review the allowed means for cancer care. In addition the impact of AROME guidelines on health outcomes will be the ultimate criterion by which our guideline should be confronted and further ameliorated in future updates.

Conflicts of interest

The authors state no actual conflicts of interest.

Reviewers

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Acknowledgement

The authors would like to acknowledge Frances Godson for the English review.

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