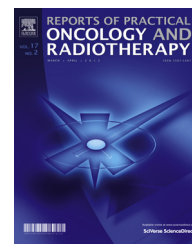


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Review

Global radiation oncology waybill

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ABSTRACT

Background/aim: Radiation oncology covers many different fields of knowledge and skills. Indeed, this medical specialty links physics, biology, research, and formation as well as surgical and clinical procedures and even rehabilitation and aesthetics. The current socio-economic situation and professional competences affect the development and future of this specialty. The aim of this article was to analyze and highlight the underlying pillars and foundations of radiation oncology, indicating the steps implicated in the future developments or competences of each.

Methods: This study has collected data from the literature and includes highlights from discussions carried out during the XVII Congress of the Spanish Society of Radiation Oncology (SEOR) held in Vigo in June, 2013. Most of the aspects and domains of radiation oncology were analyzed, achieving recommendations for the many skills and knowledge related to physics, biology, research, and formation as well as surgical and clinical procedures and even supportive care and management.

Results: Considering the data from the literature and the discussions of the XVII SEOR Meeting, the “waybill” for the forthcoming years has been described in this article including all the aspects related to the needs of radiation oncology.

Conclusions: Professional competences affect the development and future of this specialty. All the types of radio-modulation are competences of radiation oncologists. On the other hand, the pillars of Radiation Oncology are based on experience and research in every area of Radiation Oncology.

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1. Background

The term ‘waybill’ is literally a document used by a haulier providing detailed instructions related to the sending of a merchandize shipment. Nowadays, this term is also used

in order to uneventfully establish the steps required to perform a great social, human or universal task. In this article we would like to describe our ‘waybill’ for radiation oncology considering our goals step by step and taking into account the current global economic crisis around the world. As in a ‘waybill’, some instructions are

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needed to accomplish these tasks and these are described below.

1.1. The mission of radiation oncology

Radiation oncology is a speciality involving medical, technical, surgical and clinical praxis, research, teaching, and management functions.

The clinical aspects involve the treatment of different tumours by multidisciplinary teams in which radiation oncologists offer many types of treatments also associated with the use of radiomodulators. This implies the need for continuous scientific updating and knowledge on how to manage all the resources available.

2. Developments in radiotherapy equipment

Recent publication by Rajamanickam Baskar 2012 confirms radiotherapy curative power.¹ Other important aspects related to radiotherapy include organ preservation, palliation of pain and, of course, an increase in survival.² More than 50% of cancer patients receive radiotherapy, and there has been a rise in the use of this therapeutic approach in benign diseases.^{1,2}

If the 20th century played an important role in the development of radiation oncology,³ the progress in technology to date in the 21st century has been impressive with regard to precision, verification and quality assurance, allowing adaptive treatments, dose escalation and a reduction in early and late complications. The advances in morphological and functional images have contributed to the improvements in each modern radiotherapy technique. Indeed, we can expect the use of hybrid positron emission tomography/magnetic resonance (PET/MR) equipment for treatment planning in the forthcoming future.⁴

Despite having initially been developed at the end of the last century, the use of intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), adaptive radiotherapy and stereotactic body radiotherapy (SBRT) has not been extensive until now. In 2012 Milano reported a 2- and 5-year survival of 74 and 47%, respectively in oligometastatic breast cancer patients treated by SBRT.⁵ Recent advances, including continuous registry of movement control, elastic fusion, 4D treatment delivery, and different dose plan summation systems, have also been commercialized by different companies.^{4,6}

A report from the Department of Health Cancer Policy Team in the UK in 2012 concluded that initiation of radiotherapy within 31 days after achieving the diagnosis saved 2500 lives per year.⁷ Recent data from Burnet et al. indicate that improvement in survival could reach 25%.⁸ The Australian Cancer Council estimated that over a period of 10 years (1996–2006), almost 51,000 cancer patients eligible for radiotherapy did not receive it, representing nearly 40,000 years of life lost to cancer patients overall.⁹

2.1. Verification and quality control

Since the development of IGRT, better tumour and OAR definition and treatment delivery control are assets which may be incorporated into daily practice. IGRT is a verification and quality control measure. Despite the implementation of regulatory laws to control the clinical steps from the diagnosis to treatment delivery in different European countries, including Spain,¹⁰ technological advances develop more quickly. Quality control using treatment protocols has shown an impact on patient survival, however, there is a need for protocols adapted to the new technological developments.^{11,12} Patients are more controlled when included in protocols, clinical trials and guaranteed quality programmes.

3. Radiomodulation: physical, chemical and biological

Radiomodulation in radiotherapy is the concurrent addition of treatments: pharmacological, chemotherapeutic, biological, or physical to be able to change the effects of radiation to enhance the healing effect or protection of patients.

3.1. Physical radiomodulation

IMRT allows precise dose treatments protecting healthy tissues, with an escalation in dose having an impact on the gain in the therapeutic ratio with a reduction in acute and late toxicity in almost all tumour sites.^{13–20} One of the most frequently studied and reported tumour sites that show important benefits with IMRT is nasopharynx carcinoma; the reduction obtained in xerostomia results in an increase in quality of life and local control with the most frequent type of relapse being distant metastasis.^{21,22} Hypofractionation has provided promising results in breast and prostate cancer, and its use is being extended to treatments involving a reduction in the overall treatment period with a subsequent impact on the waiting lists of Radiation Oncology Departments.^{23,24} The use of IGRT for treatment delivery is becoming increasingly necessary. The association of IMRT, IGRT and 4D has demonstrated a reduction in toxicity and an increase in overall survival in lung cancer.^{25,26} Software allowing deformable fusion of geometry for volume definition in treatment planning and for image-guided treatment delivery provides better knowledge of the dose administered to the tumours and organs at risk.²⁷

Protons have also shown excellent results in uveal melanoma. The results of prospective and retrospective series comparing proton versus uveal plaques showed better results with the former at 5 years (92–99% vs. 81–96%, respectively).²⁷ In chordomas and chondrosarcomas, a higher radiotherapy dose is allowed with a dose reduction in healthy tissue.²⁸ Benefits have also been reported in children in need of craniospinal irradiation considering the reduction of the dose in the exit field. Considering the cost of these machines and the number of patients benefiting from them, one proton accelerator per 10 million inhabitants seems reasonable.

Brachytherapy developed after the discovery of radium has greatly improved. Following the development of several software, high-dose rate (HDR) sources and source projectors,

this technique currently allows geometric and dosimetric radiation modulation. The results of fractionated HDR treatment are reportedly similar to those of low-dose rate (LDR) treatments and, moreover, allow a dose escalation with a gain in therapeutic ratio. Although HDR brachytherapy is time consuming, new trends have evolved taking advantage of the technological developments to reduce the number of fractions. Indeed, some good results have been reported in patients for prostate cancer treated with a single HDR brachytherapy dose.^{29–34}

3.2. Chemical radiomodulation

The progressive developments in the combination of chemotherapy and radiotherapy have led to this association being the standard treatment in many tumours such as the head and neck, cervix, rectum and lung, among others. Chemotherapy modulates the action of radiotherapy increasing the results of radiotherapy by different mechanisms, resulting in an increase in local control and survival depending on the tumour site. This association also plays an important role in organ preservation mainly in head and neck cancer.^{35–37} For example, the more recently developed drugs such as temozolamide or capecitabine have shown advantages in brain and Capecitabine, mainly in breast and gastrointestinal carcinomas, but even in lung cancers. One of the main advantages of these molecules is their oral intake, thereby making their administration more comfortable and reducing the ‘overload’ in the Oncology Department. Other drugs such as Zoledronic acid have demonstrated activity in radiosensitization, increasing apoptosis.^{38,39}

3.3. Biological radiomodulation

In this group of radiomodulators, monoclonal antibodies and genetic therapy play an important role as response modifiers during radiotherapy; the administration of interleukin colony-stimulating growth factors, anti-angiogenesis drugs, vaccines and non-specific immunomodulators has extended in clinical practice and trials. The most useful in several squamous tumours is Cetuximab, mainly in head and neck cancer.⁴⁰

Paediatric tumours, germinal tumours and squamous tumours seem to most benefit from these treatments. DNA repair inhibitors such as ABT-888 are under analysis in combination with whole brain radiotherapy in patients with brain metastases due to breast cancer (NCT00649207: Princess Margaret CC Trial). BSI-201, a PARP inhibitor, is also under analysis in triple-negative breast cancer associated with radiotherapy. But in a recent article in triple-negative breast cancer patients who had received radiation therapy, local control improved significantly (recurrence with RT only 4% at 5y).⁴¹

4. Support care

During the course of radiotherapy patients need symptomatic control of acute side effects. Despite the appearance of new technology and the administration of more sophisticated radiotherapy treatments, patients still present pain, increased skin damage with new targets such as cetuximab,

mucositis, anaemia and vomiting caused by different chemotherapy agents. Support care during radiotherapy is becoming more important and relief of these symptoms is part of our tasks. Nursing protocols for controlling patient symptoms and nutritional support are of help in clinical practice and, considering the concomitant use of radiomodulators, medical protocols have also been developed by MASCC and ESMO for vomiting.⁴²

5. Radiation oncology training

The future of Radiation Oncology should be considered by trainees and their needs should be taken into account. The forthcoming future should include a common part of training for medical and radiation oncologists considering that these two medical specialities will work together increasingly more closely. With the vertiginous developments in medical and radiation oncology, we can expect a strong compartmentalization by tumour sites, which will be considered as subspecialities. Taking this into account, the number of people working in oncology or in some tumour sites may be reduced. As a result medical and radiation oncologists may need to share knowledge and practices in order to be equal in many aspects of clinical practice and thereby to avoid the loss of human resources, mainly during the current world recession.

Radiation Oncology requires continuous formation following courses, meetings, work in cooperative groups and research as part of the daily tasks in this specialty. The attainment of the PhD has been simplified with the new “Reaál Decreto 99/2011” in Spain and it is considered a part of the credits obtained during formation.⁴³ Training in specific fields of radiation oncology such as brachytherapy and special techniques also requires preparation and skill, which would entail at least 5–6 years of training in the specialty.

6. Research

Research is a slow continuous process that implies a multidirectional relationship between basic researchers, applied physics, and clinical oncologists. Future developments in research will arise from precision in radiation therapy techniques, the combination of therapies with radiotherapy, nanotechnology and individualized treatment based on the prognosis of each patient. In the next years, knowledge on genetics and tumour and healthy tissue response will determine the treatment of each patient.⁴⁴

Funding in research is mainly based on the development of new drugs and treatment strategies as demonstrated by the large number of clinical trials published and ongoing. Research is limited in radiation oncology by the cost of investment in high technology and also because of the number of patients treated in a Radiation Oncology Department in clinical practice. It is, therefore, difficult to develop trials with different fractionation schedules, IMRT results, brachytherapy treatments and also comparing radiotherapy with surgery.⁴⁵ As a result of these difficulties, there is a lack of relevant clinical trials to justify the technology to the governmental health care system in many countries such as Spain.⁴⁶ The

Table 1 – Relationship between survival and distant recurrence-free interval (DRFI).

Year of diagnosis	DRFI < 3 years	DRFI > 3 years	P
1978–86	13 m	34 m	<0.0001
1987–94	13 m	33 m	<0.0001
1995–04	14 m	31 m	<0.0001
2005–10	–	32 m	–
	P = 0.15	P = 0.57	

Tevaarwerk, 2013; Ref. 53.

m: months.

research opportunity for Radiation Oncology radiomodulation is to work with new targets and new drugs as well as in treatment individualization, ideally, associated with research groups and consortia (West 2005).⁴⁴

7. Management

In the USA, 1500 people die every day due to cancer (285 in Spain). Considering the magnitude of these numbers, the cost of radiotherapy is only 6% of the overall investment against cancer.^{47,48}

Despite the large amounts of money spent on new chemotherapy agents, the advances achieved have been proportionally small.^{48,49} On the other hand, the relationship of prescription habits and determined agents with cancer is a known fact.^{50,51} Moreover, less is spent on prevention than on investigation.^{48–51} Likewise, Bailar J. stated that the reduction in mortality in cancer is mainly related to early diagnosis.⁴⁸

Interleukins such as interferon made their debut in the 80s. Nonetheless, the most relevant development during this decade was conservative treatment of breast cancer with conservative surgery plus radiotherapy, when indicated, showing similar results to those achieved with mastectomy. Gene therapy showed great advances in lymphoma in children and testicular cancer.

The investment of billions of dollars during almost 100 years of research in cancer has been very optimistic considering the results obtained. Investment in cancer usually considers the most frequent tumour sites. Survival of breast cancer has improved over time, although only in those patients with hormone receptor-negative disease.^{52,53} Table 1 shows that no general improvement in survival has been observed over the last 30 years for patients who have developed distant disease recurrence after adjuvant chemotherapy after adjusting for Distance Recurrence Free Interval (DRFI),⁵³ regardless of the year of diagnosis and treatment.

Notwithstanding, investment in new agents continues with their subsequent use leading to large expenditures which are difficult to calculate.^{54,55} Comparatively, radiotherapy allows patient cure in about 50% of cancer patients when administered alone or in association with surgery. Data published by the UK Department of Health have shown that radiotherapy represents 5% of the national investment in cancer and is considered the second treatment of choice in this disease.⁵⁶

Nowadays, high technology in radiotherapy could allow similar results to those achieved with surgery at a lower cost,

resulting in a cost/benefit relationship. As an example, for the SBRT technique in lung cancer, Table 2 shows different treatment options and their cost per year of life lived (quality of life and age were not considered: crude cost). The results show a benefit in results and in costs for SBRT. Moreover, it should be remarked that in many patients treated by SBRT, surgery is contraindicated.^{57–62}

One of the handicaps of the new technologies in Radiation Oncology Departments is that they increase the work time of radiation oncologists by 5–10% while attempting to maintain the waiting list within the RANZCR 2011 recommendations.^{63,64} Moreover, it has been estimated that from 2010 to 2020 the number of patients requiring radiotherapy will increase by 22%, with only an increase of 2% in the number of professionals available. To alleviate this situation, it has been suggested that the number of residents should be doubled.⁶⁵ Indeed, the Allen Consulting Report for the RANZCR 2012 recommended an increase of 8% in the number of radiation oncologists, 25% of technicians and 50% of physicists for 2022.⁶⁶

7.1. Management of investment

The current data provided by experts and governmental departments in Europe and the USA in relation to technological needs in radiation oncology are useful, well done, and up to date, with data on the number and type of treatment units needed per country.

In Spain, there are 5 treatment unit machines per million inhabitants (4/5 Linacs); 42% of the Radiation Oncology Departments have IMRT, although only 17.6% use this technology and 40% of the departments have brachytherapy units. However, the recommendations state that 6 Linacs should be available per million inhabitants, thus, more Linacs should be acquired in Spain and Co⁶⁰ Units and Linacs aged more than 10–15 years should be eliminated.^{67,68} Nonetheless, the number of Linacs in Spain is still not enough and should, actually, be 7 per million inhabitants, with IGRT and 2 brachytherapy units, considering that 2200 patients per million should receive irradiation and the treatment should be started in less than 31 days after diagnosis in 94% of the patients.^{69,70} The number of Linacs available depends on the country, and in the case of the Toronto area in Canada, 7.7 Linacs per million inhabitants are considered to be needed with an even higher number being considered in Australia considering the population dispersion.⁷¹ The benefits of IMRT are clear in head and neck and prostate cancer; it is considered that this technique should be used in 33% of all the treatments and in 24% of inverse plannings. The time for treatment using IMRT could be faster than 3D conformational technique depending on the unit.^{70–72,73} Table 3 shows the recommendations of the Royal Australian and New Zealand College of Radiologists for the needs of technology acquisition.

8. Recommendations for Spain

The four main pillars of our speciality are healthcare tasks, formation, experience and research, all of which also contribute to cancer cure and the development of treatment strategies

Table 2 – Cost per year of life gained according to survival at 5 years in T1-2 lung cancer.⁵⁷⁻⁶²

Treatment	Surgery	SBRT	RT	No treatment
% Overall survival	44.2	45.2	7-15%	0
Years/100 patients	221	226	35-75	0
Cost 1 patient (\$)	26,419	9551	6000	0
Cost 100 patients	264,1900	955,100	600,000	0
Cost of life-year gained (\$)	11,954.3	4226.1	17,142,86-8500	Undetermined

Table 3 – Recommendations of the Royal Australian and New Zealand College of Radiologists for the needs of technology acquisition (Aimee Lovett, 9-2-2012).

Necessary for some patients according to evidence-based results
Image-guided radiotherapy (IGRT) (2D IGRT, 3D IGRT, MRI-guided IGRT)
Intensity modulated radiotherapy (IMRT) (Linac based IMRT, VMAT, Tomotherapy)
Stereotactic radiation treatment (Linac-based SRS, Gamma Knife, Tomotherapy)
Advanced imaging for treatment planning (4DCT, MRI – CT Fusion, Fusion PET – CT)
Brachytherapy (Electronic Brachytherapy, Permanent LDR Implant, Directional LDR Permanent Brachytherapy)
Particle therapy (3D Conformal proton therapy, Intensity-modulated proton therapy, Heavy ion therapy)
Insufficient evidence to date
Motion Management (Gated Radiotherapy, Tumour Tracking)
Adaptive Radiotherapy (Adaptive Radiotherapy Procedures and Processes)

(Fig. 1). Considering these main pillars some recommendations should be strongly considered in the management of radiation oncology departments in Spain:

- Number of Linacs: 6.5 per million inhabitants.
- 1 Radiation Oncologist/140 patients (add 1 doctor for every special technique at full capacity and turn) (approx. 19 Radiation Oncologists/1,000,000 inhabitants)
- 1 nurse/400-500 patients
- 2 TER/Linac and shift.
- 1 Additional TER/brachytherapy and Simulator shifts.
- 1 TER dosimetrist/400 patients
- 1 physicist/300 patients
- 1 clinical auxiliary/300 patients
- Brachytherapy units: 2 per million inhabitants.^{74,75}
- Use of Radiomodulation (physical, chemical and biological).

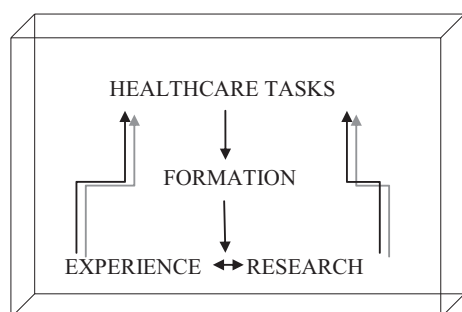


Fig. 1 – Feedback pillars of Radiation Oncology.

- Inclusion in clinical practice of new technologies that have shown good results (functional SRS, SBRT, IGRT, treatment of benign diseases, extensive use of brachytherapy in different tumour sites, etc.).
- Involvement in a plan of biological sample collection for research (i.e. blood extraction in radiation oncology outpatient departments).
- Work in multidisciplinary teams. Evidence-based guidelines are indispensable for work in different teams and for patients in need of well controlled clinical trials.
- Waiting list for starting radiotherapy: for emergencies <24 h, for urgent treatments in preferential cases <2 weeks and for ordinary patients <31 days. A reduction of the waiting list to <31 days is related to better survival.
- Radiation Oncologist Societies and administration authorities should work together to support the development of new radiation oncology centres and investment in treatment units, considering financial commitments and the economic situation of the country. Authorities, societies and industry working together could achieve a system for financing changes and modernizing the scientific park at the most opportune time.
- Scientific societies, professional colleges and authorities should work together to facilitate the best formation in radiation oncology and to establish future needs within oncological plans. In addition, promotion of the formation of radiation oncologists for research should be implemented (1 researcher per million of inhabitants), and the recommendations of societies for preclinical and clinical research should be followed.
- Close cooperation should be adhered to between different Radiation Oncology Centres, with the transfer of skills and knowledge.
- Information and counselling should be provided on the adequate use of radiotherapy to society and scientific entities.
- Simplified quality assurance programmes using a commercial workflow (i.e. similar to network Mosaiq^R Elekta Co., Aria^R Varian Co., etc.) with a no punitive system for reporting incidences should be implemented. The control of productivity using information technology software should be included in all Radiotherapy Departments.
- Resource Management units should have updated lists of costs that allow the survival of Radiation Oncology Departments adapted to the new technologies and staff needs.
- Appropriate use of IMRT for use in those patients in whom a diminution of secondary effects with impact on quality of life is expected.
- Healthcare communication programmes to increase the perception of treatment quality.
- Participation of patients in committees related to information providing and decision making.

9. Recommendations for investigation in Spain

It is essential to include basic, preclinical and clinical research in our department as recommended by the SEOR 2010.^{76,77}

Only two global, albeit laborious, recommendations:

- The inclusion of investigation in all the fields of patient care improves healthcare in 2 aspects: the application of new, very controlled concepts and the wait-and-see approach during the processes.
- Revision of the results followed by publication.

10. Conclusions

Radiation therapy should be considered essential in the control of cancer and should be part of national health planning as a major health action.

The future depends on our marketing ability which, in turn, depends on the publication of good results, and these depend on better control of our patients and the efficacy, effectiveness and cost-effectiveness which will, in turn, benefit our departments.

Conflict of interest

All authors declare no conflict of interest regarding the preparation of this article.

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