symmetry

MDPI

Article

The Choice of Gadolinium-Based Contrast Agents: A Radiologist's Responsibility between Pharmaceutical Equivalence and Bioethical Issues

Gaia Cartocci [1], Alessandro Santurro [1], Raffaele La Russa [1,2], Giuseppe Guglielmi [3,4], Paola Frati [1,2] and Vittorio Fineschi [1,2,*]

1 Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Viale Regina Elena 336, 00185 Rome (RM), Italy; gaia.cartocci@uniroma1.it (G.C.); alessandro.santurro@uniroma1.it (A.S.); raffaele.larussa@uniroma1.it (R.L.R.); paola.frati@uniroma1.it (P.F.)

2 IRCCS Neuromed, Via Atinense 18, 86077 Pozzilli (IS), Italy

3 Department of Radiology, University of Foggia, Viale Luigi Pinto 1, 71100 Foggia (FG), Italy; giuseppe.guglielmi@unifg.it

4 Department of Radiology, Scientific Institute "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Viale Cappuccini 1, 71013 San Giovanni Rotondo (FG), Italy

* Correspondence: vfinesc@tin.it; Tel.: +39-06-49912-722; Fax: +39-06-4455-335

Received: 24 October 2017; Accepted: 17 November 2017; Published: 22 November 2017

Abstract: Contrast Agents (CA) are among the most commonly prescribed drugs worldwide, and are used, with a variety of techniques, to increase and intensify the differences between body tissues and to help radiologist make diagnoses in a fast and precise way. In recent decades, advancements in research have resulted in significant improvements in their composition, and have made them safer and better-tolerated by patients; this notwithstanding, although the currently available CA are generally considered to be safe, their use is not completely without risk. The use of CA faces the radiologist with economic considerations, bioethical dilemmas, and possible profiles of professional responsibility. In fact, to achieve the best results in diagnostic imaging, radiologists have to focus on making an appropriate choice of CA, in consideration of efficacy, safety and appropriateness. Moreover, besides by cost/benefit models widely introduced in health management, radiologists are also influenced by their responsibility of appropriate use for the various diagnostic tests and, finally, the choice of best CA to utilise for each individual patient. Thus, the dilemma of choosing between the best and the most cost-effective tests and procedures is occurring more frequently every day. Different variables, such as the patient, examinations, and technology available, can affect the choice of CA in terms of obtaining the highest diagnostic quality, minimum impact on higher-risk patients, and optimisation of used volumes and injection flows.

Keywords: contrast agents; pharmaceutical equivalence; gadolinium; radiologist

1. Introduction

Since their introduction, and following their increasing use, in radiological practice over the last few decades, Contrast Agents (CA, also called Contrast Media—CM) have become one of the most commonly prescribed drugs, worldwide [1]. Nowadays, the widespread use of diagnostic imaging would be profoundly diminished without CA, because they are used, with a variety of different techniques, to increase and intensify the differences between body tissues, and to help radiologists make diagnoses in a fast and precise way [1–3]. Since CA are considered drugs, they are subjected to specific regulations and conditions. According to the European Medicines Agency (EMA) reference standards, drugs can be considered "therapeutic equivalents" if they are pharmaceutical equivalents

and if, when administered to patients under the conditions recommended in the labelling, it is possible to expect them to have the same clinical effect and safety profile [4,5]. The purpose of using equivalent drugs is mainly to directly increase competition in the global pharmaceutical market and to promote cost efficiency in sanitary management through centralised purchasing of pharmaceuticals based on competitive tenders [6].

CA should not be considered therapeutically equivalent to other drugs because they differ from each other in term of their chemo-physical structure, pharmacokinetic data, preparation modality, use precautions, therapeutic indications, and, finally, their effects on capillary permeability, microcirculation, and haemodynamics, as in the case of Gadolinium-based CA [7–9]. For these reasons, the use of CA faces the radiologist economic considerations and possible profiles of professional responsibility. The radiologist's choice of the most appropriate CA, based on correct clinical indications, but also on individual experience and evidence-based medicine, has become even more important in view of the personal liability in cases of potential adverse events and consequent litigation for CA administration. On the other hand, in cases of CA procurement and acquisition based only on economic considerations, civil and criminal liability could be assigned to the healthcare facility. Certainly, radiologists are increasingly assuming a central role balancing the need to contribute to cost containment with the need to ensure the patient's health.

2. Regulatory Framework

2.1. Definition and Use Conditions of Contrast Agents

A drug is defined as an active substance with pharmacologic activity or other direct effect in diagnosis, cure, mitigation, treatment or prevention of diseases. In the European normative framework, CA are defined as medicinal products, i.e., substances or combinations of substances that may be used or administered either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [10]. CA are largely used in clinical practice in order to support radiologists in making their diagnosis, but with no pharmacological effects in patients [11,12]; CA are defined, in fact, as "diagnostic drugs" [13]. Even though CA can certainly be identified as drugs, they have specific characteristics that distinguish them from other pharmacological preparations: CA are usually administered at high dosages, concentrations and infusion speeds (especially for X-ray techniques), and their aim is not to produce pharmacological effects.

Various types of CA have been used to improve medical imaging. Their value has been widely acknowledged, as demonstrated by their daily use in imaging departments worldwide. To obtain the best results in diagnostic imaging, radiologists have to focus on making the appropriate choice of CA, looking for efficacy (considering concentration, viscosity and osmolarity of each one), safety, and appropriateness (correct knowledge of chemo-physical and pharmacological properties, as well as the correct clinical indications). The adequate quality of a diagnostic exam is the result of a precise analysis that includes the optimisation of volume, concentration and infusion speed [14–16]. Ideally, CA should be injected and eliminated from the body without additional effects on the patient. In the past few decades, advancement in research has resulted in significant improvements in their composition, and has made them safer and better-tolerated by patients; however, the associated risks haven't been entirely eliminated. So, although the currently available CA are generally considered to be safe, their use is not completely without risk [17]. Every CA available on market needs a Community authorisation EMA following EU Regulation n. 726/2004 [18].

2.2. Pharmaceutical and Therapeutic Equivalence

To better understand the concepts of pharmaceutical and therapeutic equivalence, it is useful to specify the meaning of these terms.

Drugs with the same chemical active principles are considered "simple equivalent" (or better known as "generic"); in the case of the same biological active principles (biosimilar products), the concept of "equivalence" could be substituted also by the term "comparability". Different drugs are considered "pharmaceutical equivalents" when they contain identical active principles, dosage forms and routes of administration, and are equal in strength or concentration. This occurs for generic iodate CA used in clinical practice for Computed Tomography (CT) scans, angiographic procedures or traditional radiology, which just have to contain the same iodine concentration to be considered equivalent, since generic CA available on market have the same chemical structure, route of administration (intravenous injection) and dosage.

On the other hand, some drugs are considered "pharmaceutical alternatives" when they contain the same therapeutic moiety, but different salts, esters, and complexes of that moiety, or they differ in concentration, dosage or strength.

Furthermore, drugs can be considered "therapeutic equivalents" when they are pharmaceutical equivalents and are administered to patients under the conditions recommended by the labelling. It is possible to expect them to have the same clinical effect and safety profile.

Instead, drugs without the same active principle, either chemical or biological, which have no difference in clinical indications, efficacy or safety, are considered to be "complex equivalent", also known as "superimposable" [5,19].

3. Controversy on Therapeutic Equivalence: The Case of Gadolinium-Based Contrast Agents

The Italian Medicines Agency (AIFA—Agenzia Italiana del Farmaco) and the AIFA Technical Committee, in November 2013 and February 2014, declared that CA should not be considered therapeutically equivalent, because of their varying characteristics in terms of chemo-physical structure, pharmacokinetic data, preparation modality, use precautions, therapeutic indications and, finally, effects on capillary permeability, microcirculation, and haemodynamics of compartment distribution. Furthermore there's no evidence of head-to-head studies of diagnostic efficacy sufficient to define therapeutic equivalency [7–9]. CA, in fact, are composed of different molecules with non-overlapping chemical and physical parameters, characterised by significant differences in terms of concentration, viscosity, osmolarity and safety profile. For this reason, it's not possible to have the same correlation of "therapeutic equivalence" for CA like for other drugs; at most, those could be considered "similar", because they are not necessarily completely interchangeable [20]. These significantly different effects may suggest a preference for the use of one CA over another, depending on clinical setting, patient characteristics, and specific cases. This statement is exemplified by the case of gadolinium-based Magnetic Resonance Imaging CA (MRI-CA): after the first marketing authorisation of gadolinium diethylene-triamine-penta-acetic acid (Gd-DTPA) in 1986, other Gd-based chelates were introduced to the market. Although gadolinium is the critical element responsible for the enhancement properties of MRI, the chemical structure of the ligand determines the degree of enhancement, as well as the pharmacokinetics, charge, biodistribution, and toxicity of each specific agent. All Gd-based CA available in Europe differ from each other with respect to their physical properties as ionic vs nonionic, or are classified for clinical applications on the basis of their biodistribution and excretion as nonspecific extracellular vs tissue-specific. There are two structurally distinct categories of commercially available Gd-based CA, classified on the basis of chemical structure of the ligand as linear ("open chain") or macrocyclic [21]. In the macrocyclic structure, the gadolinium ion is "caged" in the preorganised cavity of the ligand, and the dissociation rate of gadolinium is lower than the dissociation of linear ligands, so macrocyclic CA are considered to be the most "stable" [22,23]. Stability refers to how tightly bound the gadolinium ion is to the chelating molecule, and how likely it is to dissociate. When this happens, the released gadolinium ion is picked up by a variety of competing anions and cation-binding proteins in the circulating blood. The higher the dissociation constant, the higher the possibility of dechelation and the release of free gadolinium into the body. The rate of dissociation of the complex in vivo is thought to be an important factor that determines, at least in part, the likelihood of a specific

Gd-based CA being associated with Nephrogenic Systemic Fibrosis (NSF), a serious but rare adverse event [24]. Finally, technical documentation of CA in commerce also highlights the differences between indications, contraindications and safety profiles.

On 17 March 2016, the EMA initiated a review of the risk of gadolinium deposition in brain tissue after repeated use of gadolinium CA in patients undergoing Magnetic Resonance Imaging (MRI) scans [25]. After carrying out an almost year-long in-depth review of the risk of brain deposits, and of the overall safety of these products, EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) recommended the suspension of the marketing authorisation for three linear gadolinium CA, because small amounts of the gadolinium they contain had been found to be deposited in the brain. The CA cited, all with a linear structure, were gadodiamide, gadopentetic acid and gadoversetamide.

Following the PRAC's March 2017 recommendation, some of the marketing authorisation holders concerned by this referral procedure requested a re-examination. Upon receipt of the grounds for their requests, the PRAC commenced re-examination, which concluded in July 2017, confirming its previous conclusion that there was convincing evidence of gadolinium deposition in brain tissues after use of gadolinium CA [26].

The EMA concluded its review of gadolinium CA on 21 July 2017, confirming PRAC's previous recommendation to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the authorisations of others.

The recommendations—confirmed by EMA's Committee for Medicinal Products for Human Use (CHMP)—follow a review that found that gadolinium deposition occurs in brain tissues following use of gadolinium CA. Currently, there isn't sufficient scientific evidence to affirm that gadolinium deposition in the brain has caused harm to patients; however, EMA has recommended restrictions for some intravenous linear agents in order to prevent any risks potentially associated [27].

Finally, EMA's recommendations assert that: "Macrocyclic agents have to be used at the lowest dose that enhances images sufficiently to make diagnoses and only when unenhanced body scans are not suitable". Some linear agents, however, will remain available on the market, like gadoxetic acid and gadobenic acid (linear agents used for liver scans at low doses) or a formulation of gadopentetic acid for intra-articular use, with a very low gadolinium concentration (around 200 times lower than that of intravenous products). EMA's recommendations claimed that all other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in EU member states [27]. The final recommendations will be sent to the European Commission, which will supply a final legally binding decision applicable in EU.

4. The Role of Radiologists

Despite massive developments in medicine, and progress in healthcare systems in the last few decades, the public health service is facing countless problems and health service reform is a matter of intense public debate [28,29]. Many problems in healthcare management are related to bureaucracy, mismanagement, general disorganisation, and spiralling costs [30]. Increasingly, the urge to acquire totally effective healthcare is in conflict with the limitation of resources; the issue of universal versus limited access is a new version of the antinomy between healthcare for the good of individuals and that for the good of the community [31].

Within the described scenario, radiology suffers from the same limitations as those for the whole healthcare system, i.e., expense increases, relative shortage of resources, and an increase of "waiting lists" [32]. Even though suitability and justification assessments in radiological practice are up to the radiologist, the absence of common knowledge and the lack of protocol sharing and guidelines for prescription result in a controversial state.

In the last decade, the increasing use of radiological exams in clinical routine, as well as the rising popularity of volume imaging, determined by newly available technologies, have revealed the need for common daily use of CA [33].

Thus, radiologists' needs and capabilities continue to grow in the face of constrained resources, so that every day, the dilemma of choosing between the best tests and procedures and the most cost-effective is becoming even more frequent. In fact, with increasing pressure to reduce healthcare spending, the cost-effective use of CA has become an important issue in radiology management.

While cost/benefit models have been widely introduced in health management, radiologists are more influenced by their responsibility for defining the range of appropriateness for the use of the various diagnostic tests and, finally, the best CA to utilise for each individual patient.

The need to reduce healthcare spending has led national health systems to centralise purchase tenders of drugs, so it's possible to issue a call putting in competition only different drugs with therapeutic overlap. Considering that, as shown before for Italian market, AIFA did not approve the equivalence of CA, these products should not be put in economic competition.

In particular, radiologists are faced with the task of identifying which diagnostic procedures are clinically advantageous, convenient and cost-effective, not only for the entire population, but also for the individual patient [33,34].

According to this scenario, standardised protocols require optimisation of radiation dose and CA administration to guarantee adequate diagnostic quality with low biological risk for patients, as well as the greatest possible reduction of healthcare costs. Imaging acquisition and protocol optimisation in terms of dose and CA depends, in any case, on technological improvements in scanning systems (such as the reduction-dose system), clinical indications, patient co-morbidity and CA chemo-physical characteristics. For example, contrast volume depends on patient weight, speed injection, and timing, which influence the enhancement of specific body regions or vessels, etc. [15–17]. Therefore, it appears noticeable that a correct exam execution could have a protocol standardisation based on clinical indications and patient's conditions, but indeed, these protocols have to be modified in accordance with the type of CA and scan system utilised. Radiologists have the responsibility of adjusting scan protocols and CA administration in consideration of all of the parameters listed above, to the best of their knowledge and belief.

5. Bioethical Considerations

5.1. Autonomy and Responsibility

Prescription for prevention, diagnosis, treatment and rehabilitation is a direct, specific, exclusive and non-delegable responsibility of the physician, committing his autonomy and responsibility [35]. The diagnosis and therapy is, in fact, under the direct responsibility of the physician, above all in the verification of indications, contraindications, interactions, and unpredictable individual reactions. Nevertheless, the right of the patient to refuse a treatment must always be considered.

On this ethical basis, all physicians should have full autonomy in the selection and administration of any diagnostic and therapeutic drug; consequently, radiologists should also maintain their autonomy in the selection and administration of CA. Radiologists, following the principles of autonomy and responsibility, should not be limited or conditioned in their professional prerogative by any considerations of an administrative or procedural nature [36–38]. Therefore, radiologists have the right to use the most appropriate CA for each patient, and any solution to the detriment of this principle of autonomy is not practicable, even if done in the name of economic considerations and cost-saving. Moreover, limitations in the choice of CA, based on the criterion of the lowest price, might constitute a profile of criminal and civil responsibility [39,40].

5.2. Effectiveness, Safety and Appropriateness

The prescription by the physician has to adhere to the principles of clinical effectiveness, safety, and appropriateness, and should always be based on evidence-based medicine and the best use of limited resources. CA choice also has to fulfil effectiveness, safety, and appropriateness criteria as a requirement to achieving the best result for the patient [39,40]. Primarily, chemical and physical

parameters have to be considered for their effectiveness; secondarily, considering that risks associated with CA cannot be completely eliminated, precautions have to be used and possible adverse reactions have to be considered, for safety purposes; lastly, pharmacokinetic data, preparation modality, clinical-therapeutic indications, and effects on circulation, permeability, and haemodynamics have to be considered to determine the appropriateness of CA.

Furthermore, in order to choose the optimal CA, a radiologist must consider several factors, such as:

- type of examination: the method and the most appropriate protocol according to the clinical question;
- type of technology available: the technical characteristics of the equipment and its configuration affect all parameters of the diagnostic procedure, and are cofactors of choice for identifying the correct drug diagnostic to use;
- type of patient: anamnesis is necessary to identify risk factors (allergies and kidney disease), clinical conditions and comorbidity (cancer, heart disease, diabetes), age (elderly and children), and physical constitution (body weight).

Different variables such as the patient, examination, and technology available can affect the choice of CA in order to obtain the highest level of diagnostic quality, the minimum impact on higher-risk patients, optimisation of used volumes, and optimisation of injection flows.

6. Conclusions

The purpose of using equivalent drugs is mainly to directly increase competition in the global pharmaceutical market, and to promote cost efficiency in sanitary management, with centralised purchasing of pharmaceuticals through competitive tenders. It also guarantees ease of access to healthcare for patients, who are consequently able to afford pharmacological treatment with the same efficacy and safety.

According to the ESUR guidelines recommended by EMA in clinical radiological practice [24], the radiologist has the responsibility of CA selection, as well as the indication and dose assessment. In particular, for the above-mentioned reasons, the radiologist should not be limited or influenced in their decision-making process. In fact, because of the different chemo-physical and pharmacological properties of the various CA, the radiologist's prerogative in selection and administration of the best CA for the individual patient, based on correct clinical indications, appears clearly justified. The radiologist's choice of the most appropriate CA, based on their practical experience, correct clinical indications, and evidence-based medicine, is even more important in view of the personal liability in cases of potential adverse events and consequent litigation for CA administration. On the other hand, in cases of CA procurement and acquisition based only on economic considerations, civil and criminal liability could be attributed to the healthcare facility.

Certainly, the radiologist is increasingly assuming a pivotal role over time as an intermediary actor between the need to contribute to cost containment and to ensure the patient's health.

Author Contributions: All authors contributed to the paper. Vittorio Fineschi, Paola Frati, Giuseppe Guglielmi, Gaia Cartocci, Raffaele La Russa and Alessandro Santurro conceived, drafted and revised it critically. All authors approved the present version to be published.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Beckett, K.R.; Moriarity, A.K.; Langer, J.M. Safe Use of Contrast Media: What the Radiologist Needs to Know. *Radiographics* **2015**, *35*, 1738–1750. [CrossRef] [PubMed]
2. Johnson, P.T.; Fishman, E.K. IV contrast selection for MDCT: Current thoughts and practice. *AJR Am. J. Roentgenol.* **2006**, *186*, 406–415. [CrossRef] [PubMed]

3. Bae, K.T.; Heiken, J.P. Scan and contrast administration principles of MDCT. *Eur. Radiol.* **2005**, *15* (Suppl. 5), e46–e59. [CrossRef] [PubMed]
4. EMA (European Medicines Agency). Guideline on Equivalence Studies for the Demonstration of Therapeutic Equivalence for Products That Are Locally Applied, Locally Acting in the Gastrointestinal Tract as Addendum to the Guideline on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/04/WC500225230.pdf (accessed on 24 October 2017).
5. De Rosa, M. Equivalenza, comparabilità e sovrapponibilità terapeutica: Mettamo un po' di ordine. *GRHTA* **2014**, *1*, 25–30.
6. CREA Sanità (Consorzio per la Ricerca Economica Applicata in Sanità). Opportunità e Criticità della Equivalenza Terapeutica: Una Analisi Multidisciplinare. Available online: http://www.camera.it/temiap/allegati/2016/09/05/OCD177-2317.pdf (accessed on 24 October 2017).
7. AIFA (Italian Medicines Agency). Equivalent Drugs. Available online: http://www.aifa.gov.it/medicinaliequivalenti (accessed on 24 October 2017).
8. AIFA Technical Committee. Agenda Meeting of the 6-7-8 November 2013. Available online: http://www.agenziafarmaco.gov.it/content/commissione-tecnico-scientifica-cts-%E2%80%93-ordine-del-giorno-riunione-del-6-7-8-novembre-2013 (accessed on 24 October 2017).
9. AIFA Technical Committee. Agenda Meeting of the 10-11-12 February 2014. Available online: http://www.agenziafarmaco.gov.it/content/commissione-tecnico-scientifica-cts-10022014 (accessed on 24 October 2017).
10. Directive 2004/27/EC of the European Parliament and of the Council. Available online: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf (accessed on 24 October 2017).
11. Thomsen, H.S. For whom? *Acta Radiol.* **2013**, *54*, 473–475. [CrossRef] [PubMed]
12. Tamburrini, O.; Aprile, I.; Falcone, C.; Console, D.; Rotundo, A. Off-label use of intravascular iodinated organic and MR contrast media. *Radiol. Med.* **2011**, *116*, 1–14. [CrossRef] [PubMed]
13. Italian Legislative Decree n. 219/2006, Art. 1. Actuation of Directive 2001/83/EC (and Subsequent Amending Directives) on a Community Code on Medicinal Products for Human Use and Directive 2003/94/EC. Available online: http://www.camera.it/parlam/leggi/deleghe/06219dl.htm (accessed on 24 October 2017).
14. Andreucci, M.; Solomon, R.; Tasanarong, A. Side Effects of Radiographic Contrast Media: Pathogenesis, Risk Factors, and Prevention. *BioMed Res. Int.* **2014**, *2014*, 741018. [CrossRef] [PubMed]
15. Fleischmann, D. Use of high-concentration contrast media in multiple detector-row CT: Principles and rationale. *Eur. Radiol.* **2003**, *13*, M14–M20. [CrossRef] [PubMed]
16. Friebe, M. Computed tomography and magnetic resonance imaging contrast media injectors: Technical feature review—What is really needed? *Med. Devices (Auckl.)* **2016**, *9*, 231–239. [CrossRef] [PubMed]
17. Pomara, C.; Pascale, N.; Maglietta, F.; Neri, M.; Riezzo, I.; Turillazzi, E. Use of contrast media in diagnostic imaging: Medico-legal considerations. *Radiol. Med.* **2015**, *120*, 802–809. [CrossRef] [PubMed]
18. EMA (European Medicines Agency). Available online: http://www.ema.europa.eu/ema/ (accessed on 24 October 2017).
19. EMA (European Medicines Agency). Concept Paper on the Revision of the Reflection Paper on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Interferon Alpha or Pegylated Recombinant Interferon. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/01/WC500199346.pdf (accessed on 24 October 2017).
20. Pater, C. Equivalence and noninferiority trials—Are they viable alternatives for registration of new drugs? *Curr. Control. Trials Cardiovasc. Med.* **2004**, *5*, 8. [CrossRef] [PubMed]
21. Morcos, S.K. Extracellular gadolinium contrast agents: Differences in stability. *Eur. J. Radiol.* **2008**, *66*, 75–79. [CrossRef] [PubMed]
22. Rohrer, M.; Bauer, H.; Mintorovitch, J.; Requardt, M.; Weinmann, H.J. Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Field Strengths. *Investig. Radiol.* **2005**, *40*, 715–724. [CrossRef]
23. Ni, Y.; Bormans, G.; Chen, F.; Verbruggen, A.; Marchal, G. Necrosis avid contrast agents: Functional similarity versus structural diversity. *Investig. Radiol.* **2005**, *40*, 526–535. [CrossRef]

24. Thomsen, H.S.; Morcos, S.K.; Almén, T.; Bellin, M.; Bertolotto, M.; Bongartz, G.; Clement, O. Nephrogenic systemic fibrosis and gadolinium-based contrast media: Updated ESUR Contrast Medium Safety Committee guidelines. *Eur. Radiol.* **2013**, *23*, 307–318. [CrossRef] [PubMed]
25. EMA (European Medicines Agency). EMA's Final Opinion Confirms Restrictions on Use of Linear Gadolinium Agents in Body Scans. Available online: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Gadolinium-containing_contrast_agents/human_referral_prac_000056.jsp&mid=WC0b01ac05805c516f (accessed on 24 October 2017).
26. EMA (European Medicines Agency). PRAC Confirms Restrictions on the Use of Linear Gadolinium Agents. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500230928.pdf (accessed on 24 October 2017).
27. Gulani, V. Gadolinium deposition in the brain: Summary of evidence and recommendations. *Lancet Neurol.* **2017**, *16*, 564–570. [CrossRef]
28. Ottolini, F.L.; Buggio, L.; Somigliana, E.; Vercellini, P. The complex interface between economy and healthcare: An introductory overview for clinicians. *Eur. J. Intern. Med.* **2016**, *36*, 1–6. [CrossRef] [PubMed]
29. Guglielmi, G.; Nasuto, M.; Pinto, A. Forensic and medico-legal radiology: Challenges, issues and new perspectives. *Radiol. Med.* **2015**, *120*, 777–778. [CrossRef] [PubMed]
30. Paterlini, M. Italy's health system reforms on hold. *Lancet* **2013**, *381*, 1085–1086. [CrossRef]
31. Roy, D.J.; Dickens, B.M.; McGregor, M. The choice of contrast media: Medical, ethical and legal considerations. *CMAJ Can. Med. Assoc. J.* **1992**, *147*, 1321–1324.
32. Management in Radiology (MIR) Congress 2006. Overview of the National Health System in Italy: Reforming the System. Available online: https://healthmanagement.org/c/imaging/issue/volume-7-issue-1-2007 (accessed on 24 October 2017).
33. Scholz, K.; Wegener, R.; Lundt, S. Cost-effectiveness Contribution of Contrast Media: A Discussion of Perspectives. *Acad. Radiol.* **1998**, *5*, S385–S388. [CrossRef]
34. Gazelle, S.; McMahon, P.M.; Siebert, U. Cost-effectiveness Analysis in the Assessment of Diagnostic Imaging Technologie. *Radiology* **2005**, *235*, 361–370. [CrossRef] [PubMed]
35. European Council of Medical Order. Available online: http://www.ceom-ecmo.eu/en (accessed on 24 October 2017).
36. Lorusso, A.; Quaia, E.; Poillucci, G.; Stacul, F.; Grisi, G.; Cova, M.A. Activity-based cost analysis of contrast-enhanced ultrasonography (CEUS) related to the diagnostic impact in focal liver lesion characterization. *Insights Imaging* **2015**, *6*, 499–508. [CrossRef] [PubMed]
37. Awai, K.; Takada, K.; Onishi, H.; Hori, S. Aortic and hepatic enhancement and tumor-to-liver contrast: Analysis of the effect of different concentrations of contrast material at multi-detector row helical CT. *Radiology* **2002**, *224*, 757–763. [CrossRef] [PubMed]
38. Duerden, M.G.; Hughes, D.A. Generic and therapeutic substitutions in the UK: Are they a good thing? *Br. J. Clin. Pharmacol.* **2010**, *70*, 335–341. [CrossRef] [PubMed]
39. Romanini, L.; Brunese, L.; Grassi, R. *Diritto alla Scelta Libera e Consapevole dei Mezzi di Contrasto in Radiodiagnostica*; SIRM Documents; Italian Society of Medical Radiology: Naples, Italy, 2015.
40. Buccelli, C.; De Ferrari, F.; Ricci, P.; Arbarello, P. *Selection of Contrast Agents. Opinion of the Italian Society of Forensic and Insurance Medicine*; SIRM Documents; Italian Society of Medical Radiology: Naples, Italy, 2010.