

Section 1: General Principles of Care of Uncommon Cancers

1 A Structured Approach to Uncommon Cancers

Derek Raghavan

Levine Cancer Institute, Carolinas HealthCare System, Charlotte, North Carolina, USA

Introduction

Increasing attention has been focused in the past decade on the plight of patients with rare or uncommon tumors, with the emerging recognition that patients and families struggle with the additional fears and frustrations engendered by lack of easily available, comprehensive, and clear information, lack of certainty and clinical experience on the part of their medical attendants, paucity of established, recommended regimens and clinical trials, and increased costs associated with lack of defined pathways among payers. The implicit socioeconomic issues are addressed in Chapters 2 and 3.

It is also important to define a generic clinical management structure that covers any patient who presents with a rare or uncommon malignancy, as the basic principles of diagnosis, treatment, and follow-up are essentially transferable.¹⁻³ There is no complete consensus on what constitutes a rare or uncommon cancer, although commonly accepted definitions in the range of 6–15 new cases/100,000 population per year have been proposed.^{4,5}

Greenlee *et al.*⁴ have suggested that 25% of new cancer cases represent the composite of uncommon cancers, but this figure is inflated as their definition sets the criterion for “uncommon” at 15/100,000. With this definition, testicular cancer would be viewed as an uncommon cancer, and this does not really make sense. For practical purposes, tumors with an annual incidence of less than six new cases per 100,000 of population can arbitrarily be viewed as appropriate for consideration in this discussion.⁵ It should, however, be noted that this definition is still incomplete as it does not take into account the rare subtypes of common tumors. For example, although cancers of prostate and bladder are common, their small cell variants, representing incidence figures of less than 6/100,000 population per year, are definitively rare.

As noted in Chapters 2 and 3, there is remarkably little definitive information about the diagnosis and management of most uncommon malignancies. This, in turn, has led to a proliferation of single, and anthologies of, case reports, leading to a serious lack of clinical or statistical power in the definition of these entities and their treatment outcomes. Issues of concern, in these anecdotal series, include lack of pathological and staging review, widely variable treatment approaches, undefined levels of expertise of the reporters, case selection bias, and positive reporting bias. Added to this is the potential for data dredging or recycling in the various reviews of literature that frequently accompany isolated case reports.⁶

This simply underscores the importance of national and/or international cooperative trial group efforts in setting uncommon malignancies into a more prominent place in their respective research agendas, thus leading to the development of well-defined, evidence-based diagnostic and treatment pathways. The European oncology community is attempting to systematize its approach through an integrated system of websites and innovative trial design,^{2,3} and hopefully this will be assessed and validated in due course.

Initial steps

Clinical presentation

The nuances and subtleties of clinical presentation of uncommon tumors are beyond the scope of this brief introduction to management. However, it is important to emphasize that one of the fundamentals of clinical acumen is vested in the frequency and repetition of clinical tasks. This is not afforded by uncommon presentations of disease to generalist clinicians. Given the clustering of uncommon tumors at centers of excellence or in the practices of known

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experts, it makes sense that generalists should consider discussion with a subspecialist or referral to a center of excellence, at least for confirmation of diagnosis and a second opinion.

For example, uncommon presentations of cancer within the chest include extragonadal germ cell tumors and thymomas (characteristically found in the anterior mediastinum), as compared with neuroblastomas and paragangliomas (which are generally posterior); this may not routinely be perceived as clinically important by a physician who is unaware of the difference. Subtle clinical differences, such as the presence of gynecomastia, may sway the diagnosis in the hands of an expert, sometimes saving an extensive battery of unnecessary tests and biopsies (e.g. diagnostic confirmation by a grossly elevated serum β -human chorionic gonadotrophin may avoid the morbidity of a transthoracic biopsy). In the history-taking component, differences in family history (such as the presence of sickle cell disease) may assist in the diagnosis of renal medullary carcinoma versus collecting duct carcinoma when considering uncommon presentations of renal carcinoma.⁷ This textbook is replete with similar examples, and the importance of clinical acumen and experience cannot be underemphasized in designing optimal management pathways for uncommon malignancies.

Pathology review

When a patient presents with an uncommon malignancy there are a number of initial steps that should be taken, irrespective of whether the clinician is an isolated practitioner with little hands-on experience or a so-called “expert” at a center of excellence. Review of the pathology specimens in this context, by an expert, subspecialty tumor pathologist, is essential to ensure that the correct entity has been identified, so that the patient can be directed toward an appropriate management pathway or algorithm.^{1,8}

As there are few, if any, tumor pathologists who specialize in the generic class of uncommon malignancies per se, it makes sense to direct specimens for review by a well-respected tumor pathologist with a focus on cancers arising at the site of origin – for example, a genitourinary tumor pathologist for the uncommon variants of cancers of bladder, prostate, kidney, testis, and other less common sites in the genitourinary tract; a specialist breast cancer pathologist for the uncommon variants of that disease; and so forth. For example, the difference between an undifferentiated, Gleason grade 5+5 adenocarcinoma of the prostate and a small cell anaplastic prostate cancer can be subtle, and may present a real diagnostic dilemma. Similarly, the distinction between less differentiated variants of uncommon kidney cancers can be nearly impossible morphologically.

Since the advent of the molecular revolution, the assessment of genetic abnormalities associated with cancer, including alterations in the levels and patterns of expression and the elaboration of downstream products and receptors,

has become a crucial part of diagnosis. The accuracy and reproducibility of the tests that identify receptors, such as the epidermal growth factor receptor and others that might code for activity of trastuzumab and similar targeted therapies, has become an increased focus of interest. There may be discrepancies between the technologies employed – in this specific instance, the results from immunohistochemistry versus the more sophisticated molecular probes, such as fluorescent *in situ* hybridization, can be substantially different. In the setting of uncommon malignancies, this has become even more important, as patterns of gene expression and mutation may help to define finite differences between different uncommon histological subtypes. In some instances, these patterns may identify potentially druggable therapeutic targets, particularly useful when no standards of care apply.

For example, molecular and cytogenetic studies have explained how renal medullary cancers may occur in white populations without sickle cell disease, as well as the heterogeneity of their response to tyrosine kinase inhibition.^{7,9} In a similar context, there is now evidence of PD-L1 expression in collecting duct carcinomas, suggesting a possible role for the targeting of PD-L1 for this uncommon kidney tumor.^{9,10}

Potential practical impediments to routine acquisition of pathology review have been identified, such as reimbursement.³ However, this step is critical for correct management, and is usually not prohibitive in cost, and we simply believe that this must occur. Most health care systems (including those within nationalized medicine programs) cover indigent populations, and for patients with limited resources and inadequate fiscal coverage, a range of alternative funding options exist.

Other diagnostic tests

Similarly, it is important to review biochemical and other serological or biomarker tests, and radiological investigations. Small, regional pathology laboratories are usually certified by government agencies, and are perfectly equipped to carry out routine and automated batteries of blood and tissue biomarker assays. In the instance of rare tumors, the relevant biomarkers and molecular probes may be unique and uncommonly assayed, and thus the quality assurance (and experience of the laboratory staff) perforce is less likely to be as robust. Thus it behooves the careful clinician to ensure accuracy of test production and interpretation for uncommonly used assays.

By analogy, diagnostic radiological workup of uncommon tumors may be challenging for the less experienced general radiologist or oncologist, and it is worth ensuring review at a center of excellence with experience in radiological presentations of uncommon tumors. As noted in Chapter 6, radiological assessment of a primary urachal tumor (as compared with local extension from a prostate or colorectal malignancy, or an artifact from a recent transurethral biopsy of the dome) can be a challenge for a diagnostician inexperienced in this problem.

Review of published experience

Because of the paucity of peer-reviewed, published information regarding optimal approaches to diagnosis and management of these conditions, it has been proposed that there should be more publication of small case series or even isolated case reports,³ a view with which I strongly disagree. Series of clinical anecdotes, without the benefit of pathology and diagnostic testing review, often written by junior and inexperienced physicians, occasionally augmented by inadequate literature reviews, would not be expected to provide a reliable guide to optimal care for these patients. This situation may become worse with the proliferation of open-access publications, some of which are desperate for content, and with relatively scant quality assurance processes. Also of importance, the conventional medical literature has an emphasis on “positive” reporting, thus selecting out reports of treatments that have not been successful.

That said, there is certainly useful information available to clinicians on the internet, particularly in the PubMed website (which has standardized criteria for the inclusion of journals that require peer review of content). The quality of the information can most usefully be discerned by addressing the issues discussed above – viz. case load, central pathological review, reporting of all cases, criteria of assessment of treatment response, and clarity of outcomes presented.

As noted in Chapters 2 and 3, patients and their families, when faced with these rare tumors, and a relative lack of medical support and experience, may turn to the internet or other unconventional sources of information, and may be influenced by anecdotes or advertorials that are not supported by real data. Thus, as fastidious clinicians, we should support actively the information sources that will provide useful information to our patients and their families, in addition to providing guidance to clinicians.

Two definitive texts (this and four previous editions of *Textbook of Uncommon Cancer* since 1988¹¹ and the French language publication *Tumeurs Malignes Rares*¹²), have been developed for clinicians (but de facto also for patients) in an attempt to address some of these issues, but have not been able to cover all relevant topics in the detail needed by the clinician faced with every complex and rare condition. Increasingly, the standard oncology texts are beginning to address the more interesting or therapeutically responsive rare cancers, but also fall short on issues of detail and in providing completely current information.

Another potential source of information is the Rare Cancer Network,¹³ founded in 1993 in Lausanne, Switzerland, by Professor Rene Mirimanoff, with data generated by email and a dedicated website, but apparently absent central histological review. This group has summarized its work in a recently created open-access journal, and while worthy in intent, interpretation of some of their outcomes is confounded by factors listed above and, in particular, the issue of centralized quality assurance. That said, a recent consensus meeting, established under the auspices of the European Society for Medical Oncology, has attempted to address many of these issues, leading to the updated

website RARECARENET (<http://www.rarecancerseurope.org/> and <http://www.rarecarennet.eu/rarecarennet/>, both last accessed October 2016).^{2,3} Of importance, this initiative has also attempted to define areas of greatest need in the uncommon malignancy domain in order to make them the objects of greater focus and stringency of data production on a collaborative basis.

In the USA, since 2013 the National Cancer Institute has listed rare tumors as one of its emerging interests, but the level of focus to date has been somewhat scanty. The relevant website (<https://ccrod.cancer.gov/confluence/display/RTIP/Rare+Tumors+Initiative+Home>, last accessed October 2106) is not especially informative. Their overarching strategy is “to take advantage of the talents of intramural investigators with expertise in genetics, genomics, proteomics, molecular biology, imaging, tumor models, pharmacokinetics, pharmacodynamics, biomarkers, and clinical trial development and execution”.

Nascent initiatives have been developed in Canada, where early-phase basket trials of targeted therapies have been conducted for patients with uncommon tumors, and in Australia (see Chapter 3). Several national initiatives have come together under the rubric of the International Rare Cancer Initiative (including input from Cancer Research UK, European Organization for the Research and Treatment of Cancer, US National Institutes of Health, National Cancer Institute of Canada Trials Group, and the British National Institute for Health Research) with the intention of developing increased focus on the plight of patients with rare tumors and ultimately launching international collaborative studies.¹⁴ A much more detailed discussion of what information is needed by patients and families, and sources of available information is presented in Chapters 2 and 3.

Co-management

In the present era, in several nations where small oncology practices are increasingly under threat from large health care systems, there appear to be negative incentives influencing the likelihood of individual clinicians to refer to major centers, thus risking the loss of potential ongoing care of the patient. This is a particularly important issue in the present context, where the optimal approach for uncommon tumors may be much less known than for common cancers – specifically, the level of expertise and access to structured approaches of routine management can be crucial.

For isolated or underinsured patients, the problems are compounded, and the ideal approach of early consultation and/or referral may reflect the added challenges experienced by these populations.^{15,16} Thus it is important for the generalist or isolated clinician to develop a personal algorithm for handling uncommon tumors or uncommon presentations of common cancers. In our view, one of the most underutilized options appears to be the leveraging of telephone or email relationships, where a clinician has the opportunity of discussing choices for diagnosis and

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management of uncommon cancers with a loco-regional or national expert. Many centers welcome this type of inquiry as a means of providing improved care and establishing relationships with potential referral sources.

When a clinician is attempting to find an expert with relevant experience, it is not difficult to identify a nationally known figure with a published track record in a specific tumor type, and these clinicians usually see a broad range of uncommon variants of tumors within their generic expertise. Sometimes, such an expert will have published specifically on the particular uncommon tumor. Review of the proceedings of national and international meetings may also identify experts in rare tumors, as do the tables of contents from some of the publications listed in this chapter.

When a clinician is attempting to identify a true expert in an uncommon malignancy, in addition to referring simply to a center of excellence with a publication record (easily identified via PubMed or other listings of peer-reviewed publications), appropriate questions to address with the putative expert may include:

- How many of these cases have you seen and/or helped to manage?
- What were the outcomes?
- Is this experience published?
- How long was the follow-up?
- Are there any other experts whom you consult?
- Do you require routine pathology review?
- Are these cases routinely presented to multidisciplinary tumor boards or conferences?

These principles of management for the generalist or isolated physician are summarized in Table 1.1.

The issues of concern that relate to potential litigation can usually be handled by the insertion of caveats into any management opinion, or even the production of written documentation that explains that the discussion produced an opinion that was theoretical or conceptual to assist in

management for a patient who was neither referred nor directly managed, and with no financial relationship. In some instances, this type of contact will lead to referral for a second opinion, and a joint decision can be made regarding management at the center or locally, or even the approach of co-management with shared decision making and oversight.

Ideally, when the isolated clinician involves a center of excellence in the provision of a second opinion, in addition to expert pathological review, there is the potential for use of molecular diagnostic techniques that may identify a suitable target for systemic therapy if there is no established standard of care. In recent times, the National Cancer Institute of Canada has been conducting a phase II umbrella trial in which sunitinib or temsirolimus are being evaluated against a range of uncommon malignancies, which may share expression of gene aberrations that lend themselves to tyrosine kinase inhibition.¹⁷ Given the slow rate of progress in the evolution of systemic therapies for advanced uncommon cancers, it seems most likely that this approach may lead to meaningful progress in the next few years.

Recommendations

The management of uncommon tumors is a challenging and demanding domain, both for the less experienced clinician and for patients and families. Although resources exist that will allow self-learning and evolution of approaches to management, we believe that it is more efficient and more effective for the isolated or less experienced clinician to involve an expert or a center of tumor-specific excellence in the development and implementation of a management program for a patient with an uncommon malignancy. In some cases, specific subspecialty care may be required (especially in the domain of surgical oncology), but most

Table 1.1 Schema for the management of uncommon tumors.

Steps in management	Rationale
Confirm histological diagnosis – by expert tumor pathologist Review of radiology and other diagnostic criteria (including unusual biochemical or gene tests) Literature review: • Standard texts may have relevant sections • Consider <i>Textbook of Uncommon Cancer</i> or <i>Tumeurs Malignes Rares</i> (note selection biases and potential dated information in any text) • PubMed or equivalent (problems summarized in text) Consult an expert – usually at a center of excellence, choosing an expert with a relevant publication record or presentation record at national/international meetings Practical consideration: set up a partnership with an expert	Extensive literature supports benefits of pathology review in centers of excellence; even more important in cases of rare malignancies Uncommon findings can easily be misinterpreted, including radiology, biochemistry, and molecular testing; quality controls may be less rigorous in this context, outside centers of excellence Textbooks are usually written by experts with extensive experience in the management of specific cancers, and sometimes include uncommon patterns of presentation or rare tumors. Beware isolated case reports for inaccuracies noted in text of this chapter; beware data recycling in reviews; beware the “case report and review of the literature” Rare tumors tend to cluster at centers of excellence, at least to the extent that expert opinions will be sought and pathology/scans reviewed It may not be feasible for a patient with an uncommon cancer repeatedly to attend a center of excellence, but the expertise of such a center (including pathology and staging review) can often be shared in an active partnership with a local oncologist providing specific treatment pathways, follow-up and data for the center.

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cases of radiotherapy or systemic treatment can readily be handled by the oncologist of first contact, provided that this is done according to a well-defined management plan, and in collaboration with an experienced clinician or center. This approach places patient welfare at the center of the algorithm.

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