Lessons learned from the study of soft tissue sarcoma

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ABSTRACT

Soft tissue sarcoma is a rare disease. We began a prospective database for in-patients treated on the surgical service at Memorial Sloan-Kettering in 1982. We now celebrate 30 years of this database which has been reviewed and cataloged constantly on a weekly basis. We approach 10,000 treated patients. The study of this heterogeneous group of diverse pathology rising in the soft tissue has been fascinating. We have learned about demographics, prevalence, incidence, and have recognized the value of such databases in describing not just outcome but biology. Site is an important determinant of outcome and illustrates the complexities of including all sites in any staging system. For example, local recurrence in the extremity, while associated with a decrease in survival, is clearly not causative. Conversely, retroperitoneal sarcoma, particularly liposarcoma, is a common locally recurring disease with local progression often the cause of disease-specific mortality. Genetic predispositions have been defined. Radiation therapy and lymphedema, both alone and in combination, predispose to the development of sarcoma. These observations have important relevance as we increasingly utilize radiation therapy to minimize local recurrence in early stage breast cancer and ductal carcinoma in situ. It is clear that outcome is histology specific and wide variations in outcome, depending on the underlying histological types and subtypes, are evident. We have established very clearly that limb preservation as opposed to amputation is equally efficacious and does not diminish survival. Radiation therapy can limit local recurrence but must be balanced against side effects. Unfortunately, the majority of chemotherapeutic regimens have had minimal benefit.

It is a pleasure to be present to recognize the major contributions of Professor Renzo Dionigi. We began our commonality of interests in the late 1970s at which time we were both interested in nutritional support particularly as it relates to malignant disease.1–3 Subsequent interest diverged somewhat as Professor Dionigi made significant contributions to the immunology of infection following his time with Dr. Wesley Alexander. However, it is of interest to note that in the first decade of the 21st Century, we remain with similar interest, for example in the management of the inferior vena cava with malignant disease and the role of blood transfusion in outcome after major hepatic or pancreatic surgery.4–7 It is a pleasure to recognize Professor Dionigi and his major contributions here in Varese.

I have elected to speak about a subject that has fascinated me for the last 40 years. This year we will celebrate the 30th anniversary of the initiation of the soft tissue sarcoma database at Memorial Sloan-Kettering Cancer Center (MSKCC). This database, which I began shortly after arriving at MSKCC, is an in-patient database recording information on all of the patients admitted for surgical care. It is prospective, reviewed on a weekly basis and has provided a great source of information about the management of this complex group of diseases. We have entered over 9,000 patients (Fig. 1) with a distribution that is well known. Approximately 40% are in

Fig. 1. Soft tissue sarcoma by site. MSKCC July 1, 1982 through June 30, 2011. n = 9040. Retro-IA, retroperitoneal–intraabdominal.

the extremities and the rest distributed throughout the body. We now know a great deal about the genetic predisposition, tumors occurring in the background of neurofibromatosis, in association with Li Fraumeni syndrome attributed to mutations in the p53 gene and the interesting association of the desmoid tumor with Gardner Syndrome. Gardner is certainly of some historical interest being born in 1909 and dying in 1989. However, he reported his syndrome at the age of 80
in a journal that is no longer published! Evidence that there are still opportunities for us senior citizens to contribute!

We know that radiation exposure is an etiological agent in the development of soft tissue sarcoma and occurs in those diseases commonly treated with radiation, such as lymphoma, breast, cervical and prostate cancer. These radiation-induced sarcomas are often very difficult to deal with and the dominant histological type is a myxofibrosarcoma. It is important to recognize that the occurrence of soft tissue sarcoma as a consequence of radiation, while rare, is often underappreciated. An analysis of 16,705 patients from the Institute Curie followed with and without radiation, showed recurrence is at least ten-fold in those receiving radiation therapy, and the cumulative risk 5 in 1,000 patients at the end of 15 years. This is important as we consider the widespread utilization of radiation therapy in the treatment of ductal carcinoma in situ (DCIS), particularly in North America. One can only anticipate a further increase in this lethal disease given the marked increase in the prevalence with which DCIS is reported. For example, in 1975 the incidence was 1.87 per 100,000 and in 2004 the incidence was 32.5 per 100,000. It is also important to recognize lymphedema as a background agent in the development of angiosarcoma, first reported from Memorial Sloan-Kettering in the first edition of Cancer by Drs. Stewart and Curie followed with and without radiation, showed recurrence is at least ten-fold in those receiving radiation therapy, and the cumulative risk 5 in 1,000 patients at the end of 15 years. This is important as we consider the widespread utilization of radiation therapy in the treatment of ductal carcinoma in situ (DCIS), particularly in North America. One can only anticipate a further increase in this lethal disease given the marked increase in the prevalence with which DCIS is reported. For example, in 1975 the incidence was 1.87 per 100,000 and in 2004 the incidence was 32.5 per 100,000.

It shows marked variation in behavior. An excellent example is the disease, lymph node dissection can, in selective patients, be curative. Nevertheless, lymphedema remains even in the era of sentinel lymph node biopsy but is certainly less than it was at the time of extensive lymph node dissection and postoperative radiation. Lymphedema is seen in parasitic lymphatic obstruction, and this too can be the source of malignant degeneration to angiosarcoma. Chemical toxins, now used infrequently, have been incriminated in the etiology of soft tissue sarcoma but are a much less common event in current practice.

We have learned a great deal about the histological subtypes of soft tissue sarcomas (Fig. 2). This subject is in evolution as the entity previously considered malignant fibrous histiocytoma is considered pleomorphic sarcoma, or more commonly a variant of myxofibrosarcoma. Noted purely by the body site, the histological subtype varies with liposarcoma most commonly seen in the retroperitoneum and the majority of visceral sarcomas now considered gastrointestinal stromal tumors. Individual histological subtypes within designations showed marked variation in behavior. An excellent example is the differences seen in the subtypes of liposarcoma (Fig. 2). Disease-specific survival can vary from 90% alive to 35% alive at ten years, purely based on the nature of the underlying histological subtype. This has major implications for clinical trials as stratification is often not considered. An early recognition of the importance of histological grade allowed great prognostication based on this simple, albeit subjective, interpretation under the microscope. Nevertheless, in rare subtypes where prediction of outcome may be difficult, such observations became important. Approximately two-thirds of patients will have a high-grade lesion and one-third of patients will have a low-grade lesion, and their outcome is remarkably reflected with the high-grade lesions having approximately 50% 10-year risk of death from disease whereas the low-grade lesions approximate 10–15%.

Dr. James Ewing, the Clinical Director at Memorial Sloan-Kettering, was on the cover of Time Magazine in January of 1931, and first described the small blue round cell tumor that bears his name. We now know that the Ewing’s gene family consists of multiple different genetic aberrations which allow us to characterize tumors with a genetic signature. An excellent example of this is synovial cell sarcoma, which historically was mislabeled because of its assumed association with peripheral joints but is now defined by the presence or absence of an SYT–SSX fusion gene. This has important implications because with a genetic signature we now make the diagnosis of tumors in sites not commonly anticipated. For example, in synovial sarcoma the diagnosis has been made in prostate, lung, heart and tongue among others, based on this genetic signature. The potential for these genetic fusion genes being targets for future therapy is an important one and requires future evaluation.

As a consequence of our very significant experience, we have been able to develop prognostic predictors of outcome. It is important to emphasize that outcomes vary and predictors of outcome vary even more depending on the outcome variable considered. For example, predictors of local recurrence will differ from the predictors of distant recurrence and indeed of distant disease-specific survival (Table 1).

Lymph node metastases are rare in soft tissue sarcoma, occurring in <3% of all patients. They are more commonly seen in the epithelial subtypes but are very rarely seen in entities such as liposarcoma. There has been some debate as to the relevance of lymph node metastasis, but it is clear that in a very small subset where lymph node metastases alone are a solitary source of metastatic disease, lymph node dissection can, in selective patients, be curative. We have progressed significantly from staging and simple entities of prognostication, to the development of predictive nomograms, which are graphical representations of statistical models defining the probability of outcome based on patient-specific entities or following specific treatment. These nomograms require large datasets and significant events both negative and positive. Combined with adequate length of follow up they can be powerful tools for predictive outcomes for individual patients. Nevertheless, they require defined populations, defined outcomes, known risk factors and require once established, validation in other datasets. This we have utilized for validation. Perhaps most important for this audience validation within an Italian dataset. It is important to emphasize that nomograms can be site or histology specific, they can be time altered, or they can be recurrence altered. They have the potential to allow the addition of biological variables and indeed may be tools for predicting the effects of treatment. We have further explored such association with the use of Bayesian Belief Networks.

The diagnosis and treatment of soft tissue sarcoma has certainly improved. No longer do we require major incisional biopsies with accompanying morbidity, but in the vast majority of patients diagnosis can be made histologically with a single TruCut core biopsy. Many believe that with the advent of immunohistochemistry, accurate diagnosis can be made on cytology alone. Given the importance of
molecular diagnosis, a core biopsy would appear to be the standard approach.

In terms of treatment, we have gone from an era where amputation was the standard and the only procedure, to limb-sparing procedures in the great majority (>95%) of patients with extremity lesions. It is often accompanied by radiation therapy which limits local recurrence but in randomized trials does not change survival. Local recurrence occurs in primary extremity lesions approximately 15% of the time. In those patients with isolated recurrence, they can be rescued by further procedures and the likelihood of success is determined by rapidity of recurrence and the size of recurrence at the time of diagnosis. For patients with a high-grade recurrence >5 cm occurring within 16 months, 4-year disease-specific survival is 18%, whereas patients who develop a small low-grade recurrence within 16 months, 4-year disease-specific survival is 18%, whereas in the great majority (was the standard and the only procedure, to limb-sparing procedures approach. This approach has been widely tested but with very limited value in adult soft tissue sarcomas, has been shown to be effective in pediatric sarcomas, and has been widely tested but with very limited value in adult soft tissue sarcoma.

Once again, it is a great pleasure to be able to present this brief lecture on a subject of interest to me to honor the many achievements of Professor Renzo Dionigi.

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References