Chapter

Appendiceal Neuroendocrine Tumors and Anorectal Melanoma

Marco Clementi, Renato Pietroletti, Andrea Ciarrocchi, Federica d’Ascanio, Guido Rindi and Francesco Carlei

Abstract

Tumor growth and spread are a complicated matter and are the result of many interconnected factors. The analysis of patterns emerging from highly numerous populations might help shed some light on such an intricate mechanism. In this respect, our studies are mostly based on the SEER database, a nation representative dataset collecting data regarding the US population, over a very long time span. This approach is revealed to be particularly useful for rare tumors, as prospective studies are not feasible. Here, we present the results and the clinical implications of our inquiries: we show the impact on overall survival of several morphological and demographic characteristics of various malignancies including anorectal melanoma and neuroendocrine tumors of the appendix. The impact of surgical treatment is discussed as well. Finally, we endorse the need to find more reliable markers of tumor biology, such as genetic patterns, to tailor an effective multidisciplinary treatment.

Keywords: neuroendocrine tumors of the appendix, anorectal melanoma, multidisciplinary treatment, lymph node spread, carcinoid tumors

1. Introduction

Tumor progression is the result of several complex and interrelated mechanisms. Apart from stage of the disease, biologic features of the neoplastic cell play a relevant role. Size, location, grading, cell differentiation, genotype mutation, and expression of oncogene are well-known features of the primary tumor all responsible for tumor progression and disease aggressiveness. Progression of the disease may occur either as a result of local growth and invasion or by means of distant spread of the disease in targeted organs via lymphatic or venous outflow. The two phenomena are a consequence of specific biologic features of the neoplastic cell and thus may occur independently from each other.

Rare tumors are particularly difficult to investigate, since prospective analyses are not easy to plan due to the small number of patients observed and treated. Therefore, reliable prognostic information are lacking or are controversial. Neuroendocrine tumor in general and those located in the appendix in particular are subjected to several controversies. Size and histology of appendiceal carcinoids, for instance, seem to influence heavily lymphatic spread and thus prognosis. Surgical strategy is debated in consequence of such features with the aim of obtaining adequate lymph node harvesting to establish a correct stadiation and prognosis.
As far as recto-anal melanoma is concerned, prognosis is very poor due to frequent diagnostic delay and rarity of the disease leading to misdiagnosis and advanced stage at presentation. However, in spite of poor prognosis, extensive surgery is still advocated although the experiences reported in the literature are very limited and sparse, undoubtedly weak to support such aggressive approach.

Thus, since high-quality data regarding rare diseases such as appendiceal carcinoids or anorectal melanoma neither are presently available nor can be obtained prospectively in a short time, a reasonable approach to partially overcome such limitations is to analyze a pool of data in large tumor registry, collecting retrospective cases. In order to maximize the statistical power of the study, potential confounders by means of multivariate analysis must be taken into account. Mathematical models can be adopted to achieve such a goal; in particular Cox regression models or matching populations by the propensity score can be successfully adopted. Populations can be described by using descriptive statistical methods for categorical and continuous variables.

We planned a study on appendiceal carcinoids and anorectal melanoma accessing the Surveillance, Epidemiology, and End Results (SEER) database, a dataset collecting a large amount of data pertaining cancer in the US population over a time span of decades.

We were able to demonstrate the impact on overall survival of different morphological and demographic characteristics of anorectal melanoma and neuroendocrine tumors of the appendix [1–4], discussing their impact on surgical treatment and prognosis.

We accessed the SEER database to retrieve the data to analyze. Then, we selected the variables that we wanted to introduce in our models to assess their impact on survival. In any statistical test performed, $P < 0.05$ was considered significant. The covariates we focused on were demographic and morphologic. In most occasions, we retrieved data on age of the patients, gender, stage of disease, ethnicity, tumor size, and lymph node invasion.

2. Melanoma of the anorectum

Melanoma of the anorectum has a dismal prognosis since frequent early metastases make any treatment ineffective, despite a multimodal approach [5]. The rectum and anal canal represent the third most common primary site of origin [6]. The resemblance to benign common conditions such as hemorrhoids often delays the diagnosis, strongly impairing the possibility of treatment with intention to cure (Figure 1) (Table 1).

Site of origin is a determining prognostic factor for cutaneous melanoma [7]. With regard to mucosal melanomas, vulvar tumors proved a better outcome than those originating from the vagina [8]. Our interest was based on the fact that although most of the tumors arise in the anal canal, a not negligible percentage of the neoplasia is located more proximally in the rectum [9]. It seems reasonable that distal tumors could have a better prognosis, because they are clinically apparent sooner than more proximal masses. The latter, in fact, tend to become apparent only when symptoms of occlusion of the large intestine ensue. Moreover, anorectal melanomas arising in the anus/anal canal or rectum drain in different lymph node chains. To verify such hypothesis, we investigated the impact of site of origin on overall survival. Bello et al. [10] showed different patterns of local recurrence: anorectal melanoma recurred more often systemically, whereas tumors of the anal canal recurred first at inguinal lymph nodes. However, the overall survival did not vary between the groups. Our results confirmed that the site of origin along the rectum and anal canal does not influence survival ($P = 0.164$).
Stage of disease did not prove to have an impact on survival ($P = 0.880$ for regional stage and $P = 0.347$ for distant stage). However, our results should be considered with caution, given that we had to use the SEER historical stage classification to obtain data consistent through time. In fact, the TNM has been changing over time, and we decided to avoid its use, in order to not reduce the overall number of cases available for final analysis. In other studies, stage showed a significant impact on survival [11, 12].

| Category                        | P value | Hazard ratio | Confidence interval |
|---------------------------------|---------|--------------|---------------------|
| Site of origin (rectum)         | 0.275   | 1.233        | 0.845–1.798         |
| Gender (male)                   | 0.707   | 0.932        | 0.646–1.344         |
| Size                            | 0.519   | 1.000        | 0.998–1.001         |
| Race (other)                    | 0.019   | 2.291        | 1.148–4.575         |
| Race (White)                    | 0.824   | 0.945        | 0.571–1.562         |
| LN rate                         | 0.027   | 1.873        | 1.076–3.261         |
| Age                             | 0.150   | 1.010        | 0.997–1.023         |
| Surgical intervention (APR/AR)  | 0.194   | 0.783        | 0.541–1.333         |
| Stage (regional)                | 0.880   | 1.035        | 0.659–1.628         |
| Stage (distant)                 | 0.347   | 1.241        | 0.792–1.945         |
| Radiation (performed)           | 0.150   | 1.461        | 0.870–2.452         |
| Lymphadenectomy (performed)     | 0.904   | 0.977        | 0.663–1.438         |

Table 1.
Cox regression model for anorectal melanoma.

Figure 1.
Survival curve for patients affected by anorectal melanoma.
In addition, we inquired the prognostic value of locoregional metastatic lymph nodes and the impact of lymphadenectomy on overall survival. To better understand the role of lymph node metastasis on prognosis, we introduced the concept of lymph node ratio, defined as the ratio between metastatic lymph nodes and total lymph nodes harvested. This was necessary to avoid bias related to the extent of lymphadenectomy. In our series, performing lymphadenectomy did not improve survival ($P = 0.904$). This could be due to early tumor spread to distant sites, thus overcoming the potential benefits of local control. Sentinel lymph node biopsy has not proven to be useful in anorectal melanoma due to the low rate of positive findings, despite the presence of more distant metastases [13]. Therefore, lymph node spread of anorectal melanoma is far less predictable than, for example, the carcinoma of the breast.

Size of the tumor did not affect survival ($P = 0.519$), although it was previously associated with an increased risk of mesorectal and mesenteric lymph node metastases in anorectal melanoma [14]. Gender ($P = 0.707$) and age of the patient at time of diagnosis ($P = 0.150$) did not affect survival as well. Interestingly, ethnicity was found to be an independent predictor of survival ($P = 0.019$). Specifically, American Indian/Alaskan Native and Asian/Pacific Islander (other) ethnicity showed a worse outcome.

Radical surgery is the best option for cure and should be the goal of treatment [15, 16]. Optimal surgical strategies need to balance the need for radical excision including lymphadenectomy against increasing operative morbidity. Consistently with the recent literature, the type of surgical intervention was not a significant prognostic factor ($P = 0.183$). The fundamental dilemma regarding the treatment of anorectal melanoma is the choice between abdominoperineal/anterior resection and local wide excision. Previous studies suggested that aggressive treatment could provide better overall results by achieving local oncological control of the disease. More recently, another trend of treatment has been emerging. According to Matsuda et al. [17], no significant differences between the two options of treatment in terms of overall survival were apparent. Abdominoperineal resection has failed to show any advantage in terms of survival, adding a higher morbidity and poorer quality of life. Thus, local excision has now become the standard of treatment. In case of tumor recurrence, abdominoperineal or anterior resection can be performed as a salvage procedure [18, 19].

Radiation therapy did not influence prognosis ($P = 0.864$), although it has been demonstrated to provide better local control, especially in patients undergoing local excision [20]. The reason stands on the fact that multifocality of the disease and radial microscopic spread make effective radical excision difficult. Targeted or systemic immunotherapy as well as regional chemotherapy has been described to improve overall survival in patients with pelvic recurrences [21–23]. Molecular analysis of recurrence melanoma is an important factor in determining which type of therapy should be adopted [24]. However, better local control is ineffective when distant spread has occurred early in the natural history of the disease.

Interestingly, race resulted to be associated with prognosis. In particular, Spanish people showed a more than double hazard ratio of death as compared to African Americans. Although this result might be intriguing, we do not have sufficient data to discuss it, given the lack of genetic analyses regarding our series. Probably, both genetic and environmental factors may play a role.

3. Appendiceal neuroendocrine tumors

Current surgical strategy for primary neuroendocrine tumors of the appendix is mostly based on tumor size. Right hemicolectomy is warranted for neuroendocrine
tumors larger than 2 cm in diameter, whereas appendectomy alone is performed for tumors smaller than 1 cm. Patients affected by neuroendocrine tumors with a diameter of 1–2 cm are candidates for hemicolectomy in case of invasion of the cecum or mesoappendix or infiltration of the lymph-vascular system [25]. This treatment algorithm was introduced on the basis of retrospective outcome data provided by Moertel and his colleagues. The disease is usually quite indolent, and overall survival is good [26] (Table 2).

At present, there is no proof of survival benefits of right hemicolectomy compared to appendectomy alone. In one of our studies, we wanted to verify whether 2 cm is a good cutoff value for identifying the best candidates for right hemicolectomy. The indication for such a procedure in patients with neuroendocrine tumors larger than 2 cm in diameter stands on the augmented risk of visceral lymph node involvement. In fact, tumor size is a predictor of nodal spread [27]. Assuming that there may be a progression from positive lymph nodes to distant metastases, hemicolectomy is recommended to achieve oncologic radicality. It has been argued that a more extended procedure may have a staging value, but not an actual impact on survival [28].

Our data showed that the type of surgical procedure did not reach statistical significance (P = 0.513), proving that an extended procedure does not confer a survival advantage. Such findings and the indolent course of the disease suggest that formal right hemicolectomy should be performed in young healthy patients, whereas those burdened with comorbidities can be treated with appendectomy without affecting oncologic outcomes. In other words, tumor size greater than 2 cm should not be considered an absolute indication for right hemicolectomy.

In another study, we focused on the natural history of metastatic lymph nodes and their clinical impact for primary pure and mixed neuroendocrine tumors of the appendix (Figure 2). The rationale for the surgical treatment is based on the risk of lymph node spread. However, the role of such an event on the natural history of the disease is not clear. First, the survival curve of our populations showed that pure carcinoids have a better prognosis than those with mixed variants (P < 0.001). After controlling for age, sex, tumor size, surgical intervention, and lymph nodes rate, a Cox proportional hazards model showed that histology was an independent predictor of overall survival (P = 0.004). This suggested that pure and mixed carcinoids differ with respect to their biological aggressiveness. For that reason, we analyzed patients having either pure or mixed carcinoids as two distinct series.

| Interaction* (P value) | Group  | P value | Hazard ratio | Confidence interval |
|------------------------|--------|---------|--------------|---------------------|
| Gender (female)        | 0.066  | Pure    | 0.154        | 0.538              | 0.229–1.263         |
|                        |        | Mixed   | 0.347        | 1.201              | 0.820–1.758         |
| Tumor size (≤2 cm)     | 0.017  | Pure    | 0.896        | 0.937              | 0.355–2.474         |
|                        |        | Mixed   | <0.001       | 0.442              | 0.286–0.683         |
| Surgical intervention  | 0.017  | Pure    | 0.029        | 0.241              | 0.067–0.867         |
| (less than RHC)        |        | Mixed   | 0.019        | 1.675              | 1.088–2.578         |
| Age                    | <0.001 | Pure    | <0.001       | 1.083              | 1.051–1.116         |
|                        |        | Mixed   | <0.001       | 1.041              | 1.026–1.056         |
| LN rate                | 0.012  | Pure    | 0.039        | 5.295              | 1.089–25.754        |
|                        |        | Mixed   | <0.001       | 17.471             | 10.47–33.382        |

Table 2. Cox regression models for neuroendocrine tumors.
Age and surgical intervention (less than right hemicolectomy compared to hemicolec tomy or more extended procedure) were found to be independent prognostic factors for both pure ($P < 0.001$ and $P < 0.001$) and mixed carcinoids ($P = 0.029$ and $P = 0.019$). In the latter group, tumor size ($P < 0.001$) was another independent predictor of survival. It is well established that the biological behavior of mixed neuroendocrine tumors can somewhat resemble that of adenocarcinoma, therefore showing a more aggressive behavior. Lymph node rate was found to have a strong independent negative impact on survival for both pure ($P = 0.039$) and mixed neuroendocrine tumors ($P < 0.001$). Metastatic spread to lymph nodes is thus of major importance to both groups. The presence of metastatic nodes largely affects overall survival and represents a reliable clinical hallmark of the aggressiveness of these tumors.

Right hemicolectomy or a more extended procedure exerted a significant protective effect with pure neuroendocrine tumors and a negative effect with mixed neuroendocrine tumors. This controversial result could be related to the higher frequency of distant metastases in the mixed group, although we were unable to test that idea because of the limitations of the SEER database.

Our studies however suffer from several limitations due to their retrospective nature and to well-known shortcomings of the SEER database. Some data were missing, thus limiting the numerosity of the populations. Moreover, the SEER database provides only a certain type of variable and no entries regarding aspects
related to molecular biology. However, these are the best data available, when it is not feasible to design randomized prospective studies.

4. Conclusion

Tumor growth and spread are complex processes. Rare diseases are the most difficult to analyze, due to controversial issues and lack of data. Moreover, morphologic data retrieved from large databases do not always provide accurate results regarding the biologic aggressiveness and survival. Therefore, molecular biology markers and genetic profiling should be the basis of future investigations.

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